CONTENTS

The American Journal of Medicine

Vol. XII APRIL, 1952 No. 4

Editorial

The Lipid Transport Functions of the Plasma . . . . . Roy H. Turner 379

Clinical Studies

Cerebral Circulation and Metabolism in Chronic Pulmonary Emphysema. With Observations on the Effects of Inhalation of Oxygen
John L. Patterson, Jr., Albert Heyman and T. Whatley Duke 382

This paper makes the interesting point that cerebral blood flow may be significantly increased in patients with chronic pulmonary emphysema. This occurs apparently as a reflection of the dilatation of cerebral blood vessels resulting from changes in arterial oxygen tension or elevation of carbon dioxide tension consequent upon impairment of gas exchange in the emphysematous lung.

Pulmonary Function in Patients Convalescing from Acute Poliomyelitis with Respiratory Paralysis . . . . . Daniel S. Lukas and Fred Plum 388

This interesting study of the effects of residual respiratory paralysis (not always obvious to superficial inspection) following acute poliomyelitis emphasizes the importance of appropriate pulmonary function studies.

Venous Thrombosis in the Upper Extremities as a Complication of Myocardial Failure
William E. Loring 397

Dr. Loring has made a careful study of the literature on thrombosis of the veins of the upper extremity and neck as a complication of myocardial failure, adding four more cases of his own. The discussion of possible contributory factors and other aspects of this condition is well thought out and worth scrutiny.

Pulmonary Infarction Complicating Thrombophlebitis of the Upper Extremity
Clyde E. Tomlin 411

Dr. Tomlin properly calls attention to the general tendency to overlook thrombophlebitis of the upper extremities as the site of origin of pulmonary infarction. Implications of considerable clinical significance are pointed out.

Contents continued on page 5

in functional G.I. *distress*

though findings are negative, patients remain positive of their many symptoms – belching, flatulence, nausea, indigestion and constipation.

prompt and effective relief

can be given most of these patients by prescribing *Decholin/Belladonna* for alleviating spasm and stimulating liver function.

DECHOLIN® with BELLADONNA

reliable spasmolysis

The belladonna component of *Decholin/Belladonna* effectively relieves pain due to spasm and incoordinate peristalsis, and facilitates biliary and pancreatic drainage through relaxation of the sphincter of Oddi.

improved liver function

Dehydrocholic acid *(Decholin)*, the most powerful *hydro*choleretic known, increases bile flow, flushes the biliary tract with thin fluid bile and provides mild laxation without catharsis.

DOSAGE

One or, if necessary, two *Decholin/Belladonna* Tablets three times daily.

COMPOSITION

Each tablet of *Decholin/Belladonna* contains *Decholin* (brand of dehydrocholic acid) 3¾ gr., and ext. of belladonna, 1/6 gr. (equivalent to tincture of belladonna, 7 minims). Bottles of 100.

AMES

AMES COMPANY, INC · ELKHART, INDIANA

Ames Company of Canada, Ltd., Toronto

DB-1

CONTENTS

The American Journal of Medicine

Vol. XII APRIL, 1952 No. 4

Contents continued from page 3

Some Supravital Observations on the "L. E." Phenomenon
ROBERT J. ROHN AND WILLIAM H. BOND 422

In this interesting study the development of the "L. E." cells was followed by use of supravital staining methods. It could be established in this way that the inclusion body derives from a mature, autolyzed polymorphonuclear neutrophil, the phagocytic cell also being a mature polymorphonuclear neutrophil. The usefulness of the "L. E." phenomenon in diagnosis of disseminated lupus was again corroborated.

Effectiveness of Various Drugs for the Prophylaxis of Seasickness
MAJ. HERMAN I. CHINN, LT. COMDR. STANLEY W. HANDFORD, COMDR. THOMAS E. CONE, JR. AND LT. COL. PAUL K. SMITH 433

This study of the effectiveness of newer agents for the prophylaxis of seasickness, a joint effort of the Armed Forces, was impressively well planned and controlled. No preparation significantly superior to Benadryl (diphenhydramine) was uncovered but at least one equally effective prophylactic, Lergigan, was found. Important conclusions concerning mode of action could be drawn.

A Study of the Therapeutic Effects of Some Amebacidal Drugs
WILLIAM A. SODEMAN AND PAUL C. BEAVER 440

This study was made to determine the relative amebacidal efficacy of Diodoquin, Chiniofon, Milibis and Thioarsenites in a closed institution with a high incidence of Endamoeba histolytica infestation among the inmates. The usefulness of the two new agents, Milibis and Thioarsenites, was substantiated.

Review

Electrokymography. II. The Great Vessel and Auricular Electrokymograms
SIMON DACK AND DAVID H. PALEY 447

In this second review of the application of electrokymography to problems of cardiac function in the normal subject and in cardiovascular disorders, the authors discuss the findings in connection with movements of the great vessels and the auricles. Special attention is paid to valvular heart disease, congenital heart disease, aneurysm and the cardiac arrhythmias. The limitations of the method are stressed throughout but despite these limitations a great deal of information of unusual physiologic and diagnostic interest was obtained in the course of these careful observations.

Contents continued on page 7

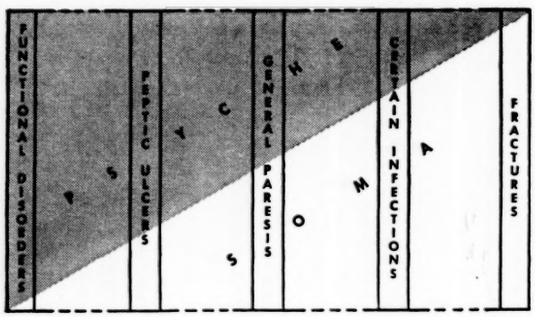
Therapy for Mixed Somatic and Psychic Complaints

Illness may be divided into:

a.) that which begins by a disturbance of function with physical breakdown (primary organic).

b.) that which begins in the psychic or emotional sphere and may eventually lead to physical breakdown (psychosomatic).

Stevenson[1] categorizes diseases according to the relative amounts of *psychic* and *physical* manifestations uncovered during interview with the patient. Burlingame's[4] classification, upon which the following chart is based, evolved from a similar thesis.



Diagnosis: people differ widely in their predisposition toward disturbances of emotional origin. The patient with greater constitutional predisposition develops illness under a relatively low level of stress; whereas the more stable individual can make good adaptation until exposed to a higher intensity of stress. For this reason examination should evaluate:

A.) Factors such as —
Emotional stability and family history.
Interpersonal relationships.
Life situations at work, in family and social areas. (Stevenson[1])

B.) *Complaints offered by patient* —
e.g. lump in throat, substernal pain, palpitation, sweating, fatigue, sick to stomach, diarrhea, menstrual irregularities.

C.) *Complaints elicited by questioning patients*—
e.g. admission of chronic anxiety, irritability, fear of illness and/or economic loss etc., difficulty in dealing with others.

D.) *Findings on examination of the patient:* muscular tenseness, moist skin, dry mouth, variable pulse rate etc. (Ebaugh[2])

Ebaugh[2] reports that somatic manifestations of such illness are intimately related to the balance between sympathetic and parasympathetic nerve tonus. Since emotions relayed via the hypothalamus, activate both adrenergic and cholinergic discharges, continuous emotional stress and anxiety result in functional disturbances.

Treatment of such conditions, therefore must be based on two methods of management:

1.) *psychotherapeutic* — to help patient adjust to stressful situations with minimal emotional trauma.

2.) *medicinal* — to relieve the patient's symptomatic distress and concern over his illness, thereby making him more amenable to psychotherapy.

Bellergal — is particularly suited as an adjunct to psychotherapy for functional disorders. MacFadyen[3] explains the rationale of this therapy as follows. Bellergal contains:

1.) *Ergotamine tartrate and Bellafoline*—these block sympathetic and parasympathetic impulses respectively, thus inhibiting transmission of stimuli which originate from emotional centers.

2.) *phenobarbital* — which inhibits the exaggerated response of the neurotic patient to stressful situations.

This combination ". . . subdues the central, sympathetic and parasympathetic activities in such a manner that the dominance of any one division is gradually decreased to a point where normal balance is re-established."[3]

BIBLIOGRAPHY

1. Stevenson, I.: G. P. *4:* 59, 1951.
2. Ebaugh, F.: Postgrad. Med. *4:* 208, 1948.
3. MacFadyen, B.: Am. Pract. *2:* 1028, 1951.
4. Burlingame, C.: Connecticut M. J. *14:* 493, 1950.

The Sandoz Scientific Department has prepared a booklet entitled *Atlas of Emotional Disorders,* useful for explaining the basic origin of functional disorders of the various systems. These are available by writing to:

Sandoz Pharmaceuticals

DIVISION OF SANDOZ CHEMICAL WORKS, INC.
68 CHARLTON STREET, NEW YORK 14, N. Y.

CONTENTS

The American Journal of Medicine

Vol. XII APRIL, 1952 No. 4

Contents continued from page 5

Seminars on Congenital Heart Disease

The Patent Ductus Arteriosus. Observations on Diagnosis and Therapy in 525 Surgically Treated Cases. . . . . ROBERT E. GROSS 472

Dr. Gross, pioneer in this field, here summarizes his experience in 525 surgically treated cases of patent ductus arteriosus, giving the clinical, laboratory and roentgenologic findings of diagnostic interest and the indications for and results of surgery. Since there are few surgical operations which, under optimal conditions, yield more gratifying results, clinical recognition of uncomplicated patent ductus arteriosus, at least after infancy, has become a must for the practitioner.

Clinico-pathologic Conference

Rapidly Progressive Hepatic Failure 483

Clinico-pathologic Conference (Washington University School of Medicine)—Fortunately, infectious hepatitis progressing rapidly to subacute hepatic necrosis is not as common a sequence as formerly but still occurs often enough to present a problem of importance. The discussion in this case brought out many of the questions that arise in such instances and reviewed the therapeutic measures undertaken to arrest the progress of the disease.

Case Report

Paroxysmal Ventricular Tachycardia and Fibrillation Due to Quinidine
MAXWELL J. BINDER AND LEON ROSOVE 491

The authors report two cases of ventricular tachycardia developing after administration of quinidine to convert auricular flutter and auricular fibrillation to normal sinus rhythm. An excellent discussion of factors which enter into such effects of quinidine follows.

Book Reviews 498

Advertising Index on 3rd Cover

Change of address must reach us one month preceding month of issue.

ROUTINE THERAPY FOR INTERNAL HEMORRHOIDS

For the vast majority of cases of internal hemorrhoids requiring conservative treatment, the employment of RECTAL MEDICONE appears clearly indicated. The enormous prescription demand which this product enjoys, furnishes definite evidence of its value in this condition—particularly so when prompt symptomatic relief is vital for the comfort and well-being of the patient.

RECTAL MEDICONE

MEDICONE COMPANY • 225 VARICK STREET • NEW YORK 14, N. Y.

to equal

the ascorbic acid content

of "Bemi.al" *Forte*

with Vitamin C.

One capsule provides

100 mg., the equivalent of

at least 24 ounces

of canned tomato juice.

This is but one feature of

"Bemina!" *Forte* with Vitamin C

which also contains therapeutic amounts

of important B complex factors.

(See formula below)

Ayerst,
McKenna &
Harrison
Limited

No. 817: Each dry powder capsule contains:

Thiamine HCl (B_1)	25.0 mg.
Riboflavin (B_2)	12.5 mg.
Nicotinamide	100.0 mg.
Pyridoxine HCl (B_6)	1.0 mg.
Calc. pantothenate	10.0 mg.
Vitamin C (ascorbic acid)	100.0 mg.

Supplied in bottles of 30, 100, and 1,000.

22 East 40th Street, New York 16, N. Y.

In addition to relief of symptoms, "All patients described a sense of well-being," said Neustaedter in reporting the effect of "Premarin" on the mood of the menopausal patient.

Neustaedter, T.: Am. J. Obst. & Gynec. **46**:530 (Oct.) 1943.

"PREMARIN"® in the menopause

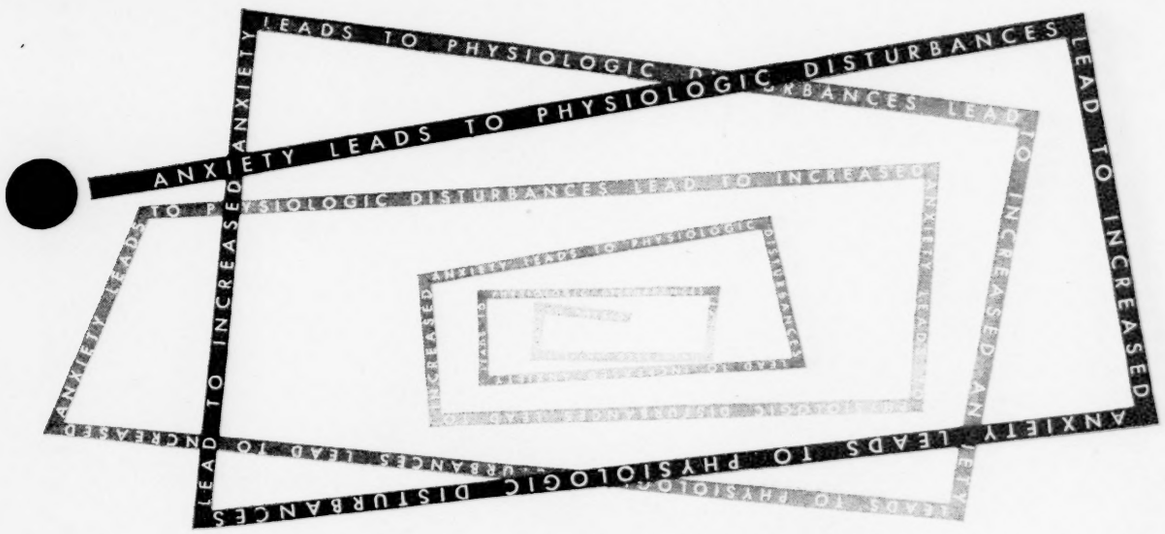
Estrogenic Substances (water-soluble) also known as Conjugated Estrogens (equine). Tablets and liquid.

Highly effective • Well tolerated • Imparts a feeling of well-being

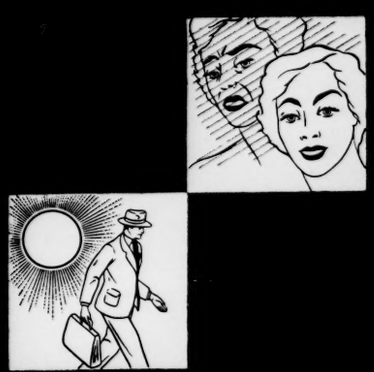
Ayerst, McKenna & Harrison Limited • New York, N. Y. • Montreal, Canada 5201

SEDAMYL

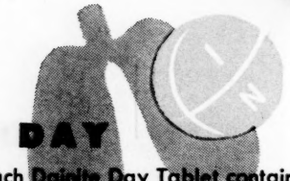
helps the patient escape from the psychosomatic maze



in anxiety states



SCHENLEY LABORATORIES, INC.,



DAY

Each Dainite Day Tablet contains:

Sodium Pentobarbital	¼ gr.
Aminophylline	3 gr.
Ephedrine HCl	¼ gr.
Benzocaine	¼ gr.
Aluminum Hydroxide	2½ gr.

NITE

Each Dainite Nite Tablet contains:

Phenobarbital	⅜ gr.
Sodium Pentobarbital	½ gr.
Aminophylline	4 gr.
Benzocaine	¼ gr.
Aluminum Hydroxide	2½ gr.

Dainite Tablets provide day and night protection for the asthmatic patient, with almost complete absence of side-effects.[1] In a series of 100 patients with bronchial asthma and pulmonary emphysema receiving Dainite Tablets on arising and retiring, only 2 patients noted nausea[1] despite the daily, full therapeutic dose of aminophylline. Marked objective improvement of respiratory function, with significant relief of wheezing, dyspnea and cough, has been observed.[1]

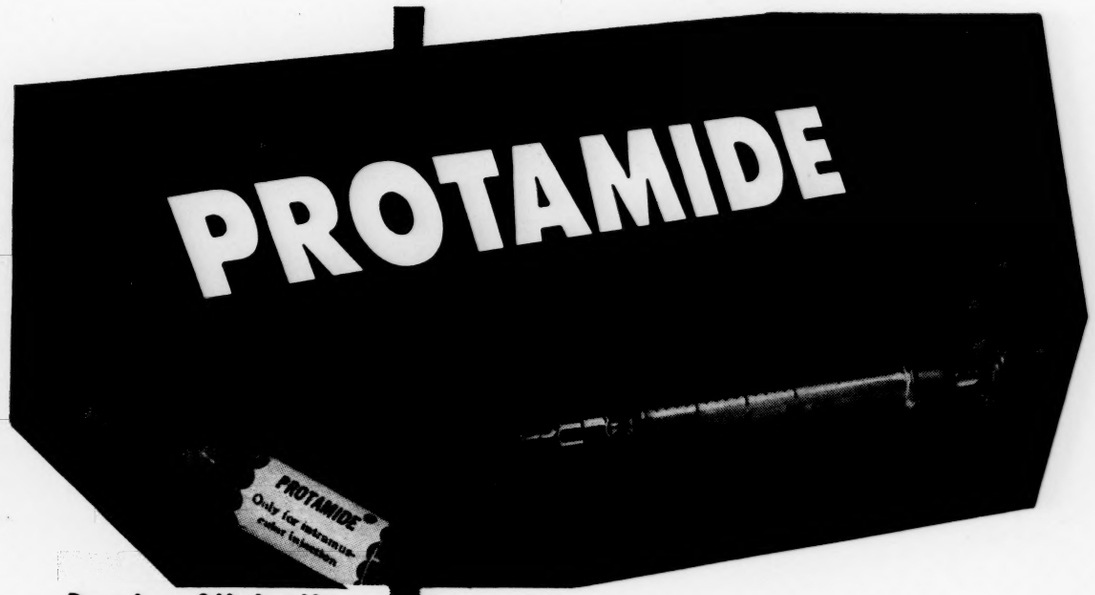
DAINITE (Irwin-Neisler) provides a night and day difference in treatment that meets the requirements of the active and the resting patient. The use of antinausea factors safely permits a more effective, prolonged dosage of aminophylline than previously available in asthmatic preparations.

Supplied as the DAINITE UNIT containing 48 Day Tablets and 18 Nite Tablets in a unique dispensing unit . . . at prescription pharmacies everywhere. **Average Dose:** One Dainite (Day) Tablet t.i.d. before meals; one Dainite (Nite) Tablet at 10 P.M.

1. J.A.M.A. 147:730-737 (Oct. 20) 1951. Literature and detailed dosage information on request.

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS

Research to Serve Your Practice



Proving Clinically that Protamide is Dramatic in the Therapy of . . . . . .

HERPES ZOSTER

The accumulated reports of the last decade from intensive investigation, give clinical evidence that Protamide has resolved the difficult therapeutic problem of herpes zoster.

These reports suggest that Protamide provides more than symptomatic relief. For example: Marsh points out that vesicles and crusts disappear much more rapidly with Protamide therapy than in untreated cases.

A significant factor in practical application is the report that Protamide is superior in the relief of pain of herpes zoster to that obtained with other commonly used treatments.

Authoritative sources also establish Protamide as non-toxic and safe [1·2] even over long periods of treatment (as in tabetic pain [2·3] management). Protamide has the advantage of comparative freedom of pain on administration[4]. Protamide is stable indefinitely.

1. *Lehman, Arnold J.; Chase, Harold F.; Yonkman, F. F.; Urologic & Cut. Rev. 43: 378 (Aug.) 1944.*

2. *Lehrer, H. W.; Lehrer, D. R.; Lehrer, H. G.; Ohio State Medical J., P. 44 (Jan.) 1951.*

3. *Costello, Russell T.; Urologic & Cut. Rev. 51:260 (May) 1947.*

4. *Marsh, W. C.; U. S. Armed Forces Med. J. 1:1045 (Sept.) 1950.*

A card or your prescription blank marked "Protamide" will bring both literature and reports.

SHERMAN LABORATORIES
BIOLOGICALS • PHARMACEUTICALS
WINDSOR DETROIT 15, MICH. LOS ANGELES

spurlos versenkt

. . . disappeared without a trace

Gelfoam

Upjohn

Bronchial Relaxant . . .
Antiallergic . . .
Expectorant . . .

Combined in a New Compound for Cough Control

Hydryllin®
COMPOUND

incorporates these important components for the treatment of cough:

AMINOPHYLLIN (SEARLE) . . . *for bronchial relaxation;*

DIPHENHYDRAMINE (SEARLE) . . . *for antiallergic efficacy;*

POTASSIUM IODIDE . . . *for expectorant action—in a pleasant-tasting syrup base.*

SEARLE

RESEARCH IN THE SERVICE OF MEDICINE

whether he is "middle-aged" or "aged"—

ORETON can be of distinct benefit

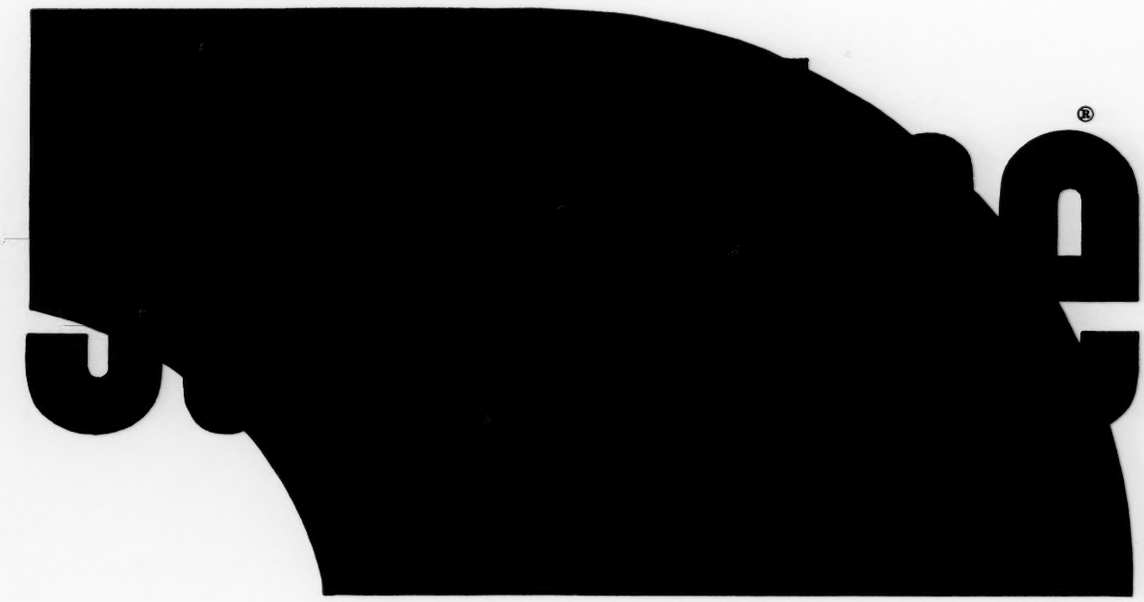
For the man of fifty complaining of climacteric symptoms, ORETON® (Testosterone Propionate U.S.P.) is indicated to overcome androgen deficiency. For the man of eighty whose strength is slowly failing, but in whom no cause other than senescence can be found, ORETON is indicated for its anabolic, tissue-building property.

ORETON

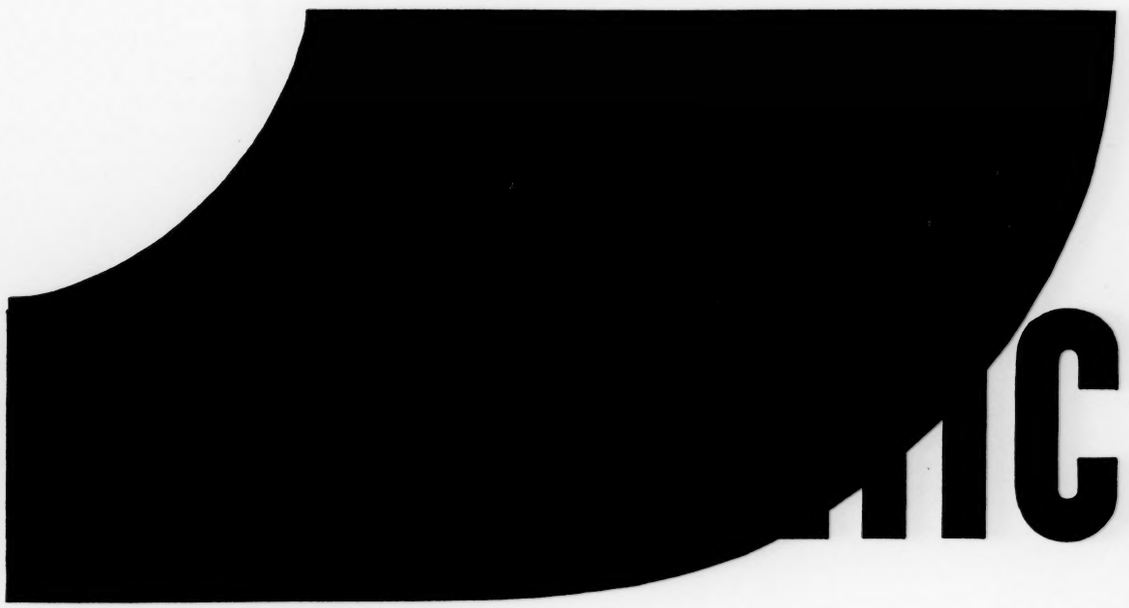
Schering CORPORATION • BLOOMFIELD, N.J.

ORETON

SA



CREMOSUXIDINE® is a smooth, delicious, chocolate-mint flavored suspension of SULFASUXIDINE®—the virtually nontoxic intestinal bacteriostat—with detoxicant kaolin and pectin for control of infectious and non-specific diarrheas. Since SULFASUXIDINE remains in high concentration in the intestines and is only sparingly absorbed, CREMOSUXIDINE is sound, effective therapy for diarrhea, even in infants and children. Supplied in SPASAVER® bottles of 16 fluidounces. Sharp & Dohme, Philadelphia 1, Pennsylvania.



for Dramatic Response...

in HYPERTENSIVE CRISES

solution INTRAVENOUS VERILOID®

A powerful hypotensive agent, Solution Intravenous Veriloid, on slow infusion by vein, is capable of dropping the blood pressure in a matter of minutes in the majority of patients.

Thus it presents a lifesaving emergency measure in the conditions in which a continuing state of extreme hypertension might lead to serious complications. Hence it has rightly been termed "A Must in Every Emergency Bag."

In hypertensive states accompanying cerebral vascular disease, in malignant hypertension, and in hypertensive crisis (encephalopathy) arterial tension can be reduced—under full control of the physician—to a point compatible with the patient's condition. The only contraindications are pheochromocytoma and coarctation of the aorta; in patients receiving quinidine therapy the drug should be given with caution.

Solution Intravenous Veriloid, 0.4 mg. of Veriloid standard reference powder per cc., is supplied in 5 cc. and 20 cc. ampules.

Solution Intravenous Veriloid makes available for the first time a purified fraction of Veratrum viride, a product of Riker Laboratories research, generically designated alkavervir, which can be administered by vein. Complete instructions for its use accompany each ampule. Physicians are invited to send for detailed literature.

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

RIKER LABORATORIES, INC.

8480 Beverly Boulevard — Los Angeles 48, California

methischol CAPSULES • SYRUP

NOW CONTAINS VITAMIN B_{12}

in coronary occlusion
hypercholesterolemia
diabetes
liver disorders
hypertension
obesity • nephrosis . . .

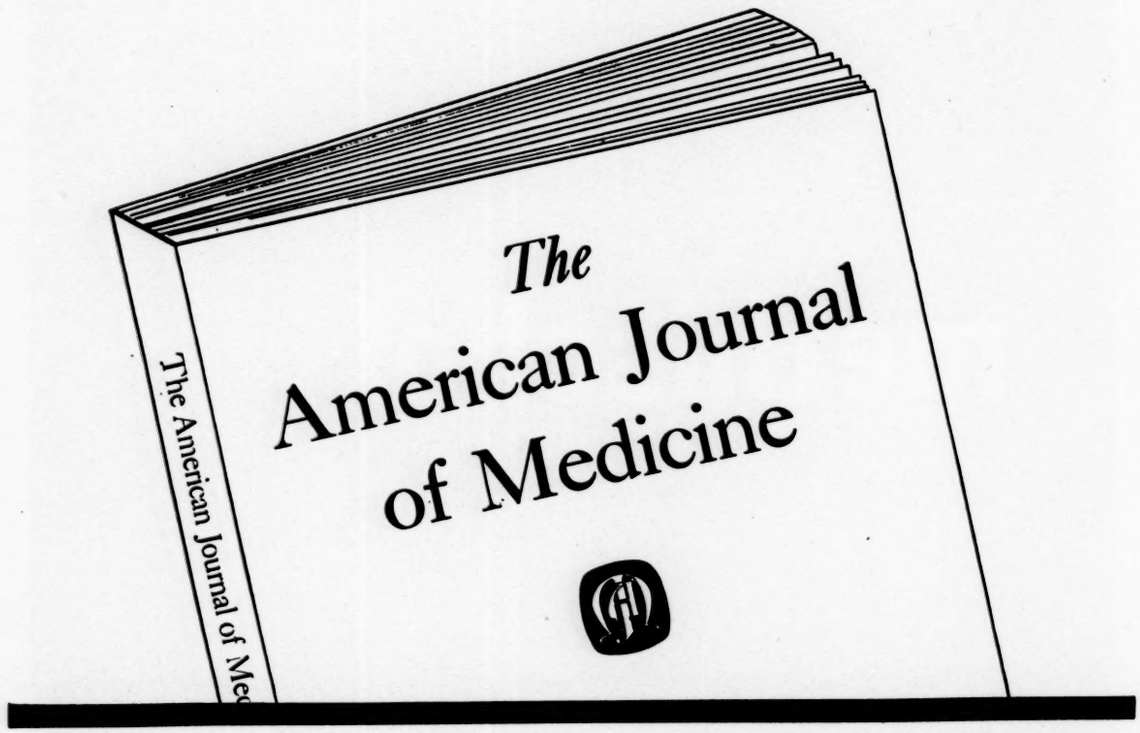
these patients deserve the potential benefits of this complete lipotropic formula . . .

helps normalize cholesterol and fat metabolism

in liver disease increases phospholipid turnover, reduces fatty deposits and stimulates regeneration of new liver cells.

Write for samples and detailed literature.

U. S. VITAMIN CORPORATION
CASIMIR FUNK LABORATORIES, INC. (affiliate)
250 EAST 43rd STREET • NEW YORK 17, N. Y.



Coming Soon!

SEMINARS WRITTEN BY INVITATION ON

PHYSIOLOGY OF THE GASTROINTESTINAL TRACT

July to December Numbers

To increase

peripheral blood flow

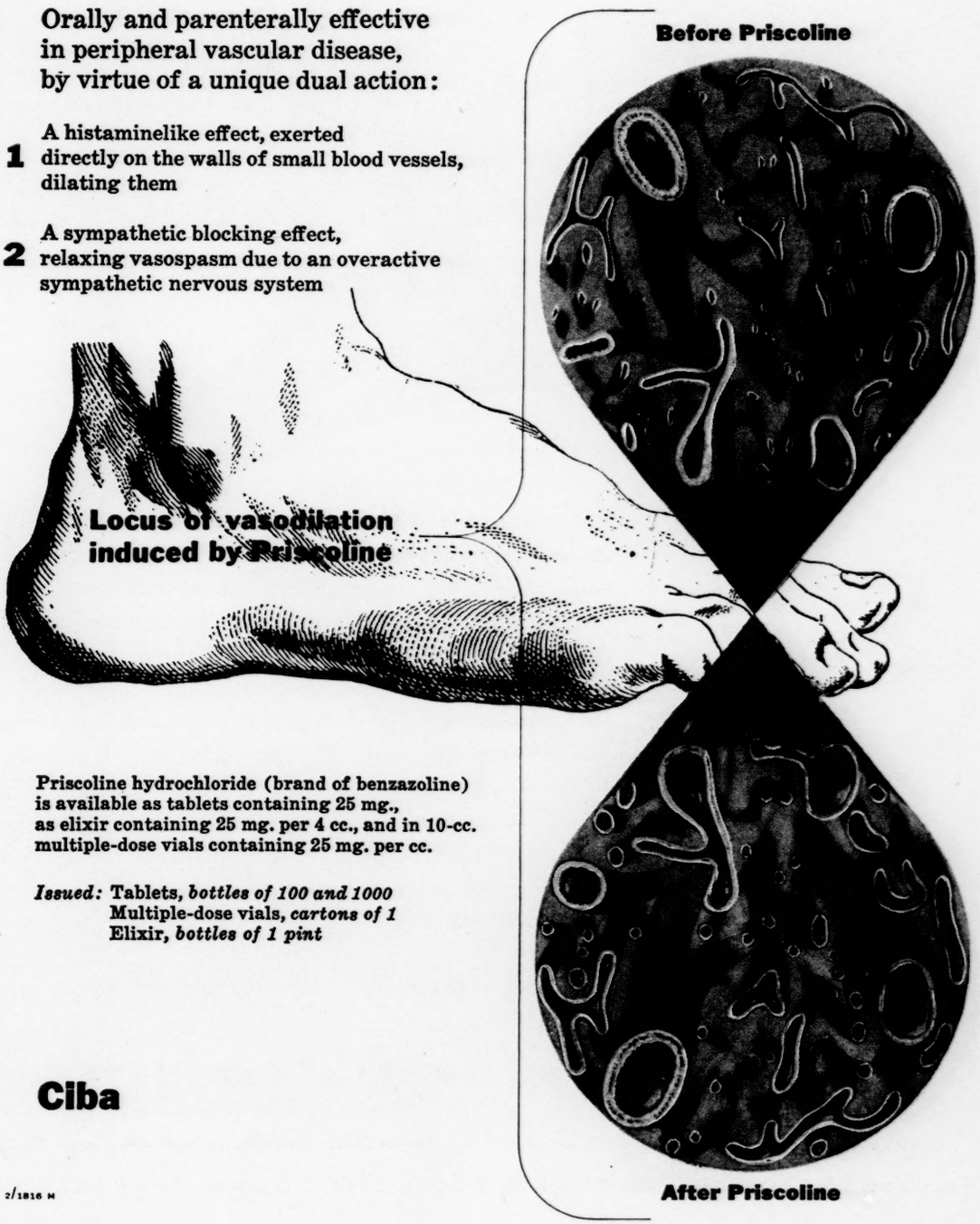
Priscoline®

a potent vasodilator

Orally and parenterally effective in peripheral vascular disease, by virtue of a unique dual action:

1 A histaminelike effect, exerted directly on the walls of small blood vessels, dilating them

2 A sympathetic blocking effect, relaxing vasospasm due to an overactive sympathetic nervous system



Priscoline hydrochloride (brand of benzazoline) is available as tablets containing 25 mg., as elixir containing 25 mg. per 4 cc., and in 10-cc. multiple-dose vials containing 25 mg. per cc.

Issued: **Tablets, *bottles of 100 and 1000***
Multiple-dose vials, *cartons of 1*
Elixir, *bottles of 1 pint*

Ciba

2/1816 M

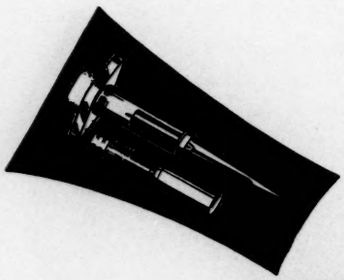
ACTHAR* *Gel*

TO FACILITATE HOME AND OFFICE TREATMENT

Specific Indications: DRUG SENSITIVITY REACTIONS following the administration of penicillin, other antibiotics, sulfonamides, etc., are specific, practical indications for the use of Long-Acting ACTHAR *Gel* in Disposable Cartridge Syringes. In these cases, the patient demands immediate and prolonged relief from the intense symptoms. ACTHAR *Gel* Long-Acting is definitely superior to conventional methods in terms of more rapid relief over greater periods of time with virtually no therapeutic failures. Low total dosage, with few injections, is required.

Supplied in a sterile 1 cc. B-D cartridge with B-D disposable cartridge syringe† in potencies of 20 I.U. per cc. and 40 I.U. per cc.

†T. M. Reg. Becton, Dickinson & Co.



*THE ARMOUR LABORATORIES BRAND OF ADRENOCORTICOTROPIC HORMONE (A.C.T.H.)

THE ARMOUR LABORATORIES

CHICAGO 11, ILLINOIS

world-wide dependability

PHYSIOLOGIC THERAPEUTICS THROUGH BIORESEARCH

a successful New product

in the treatment of allergies and dermatoses

Pyromen®

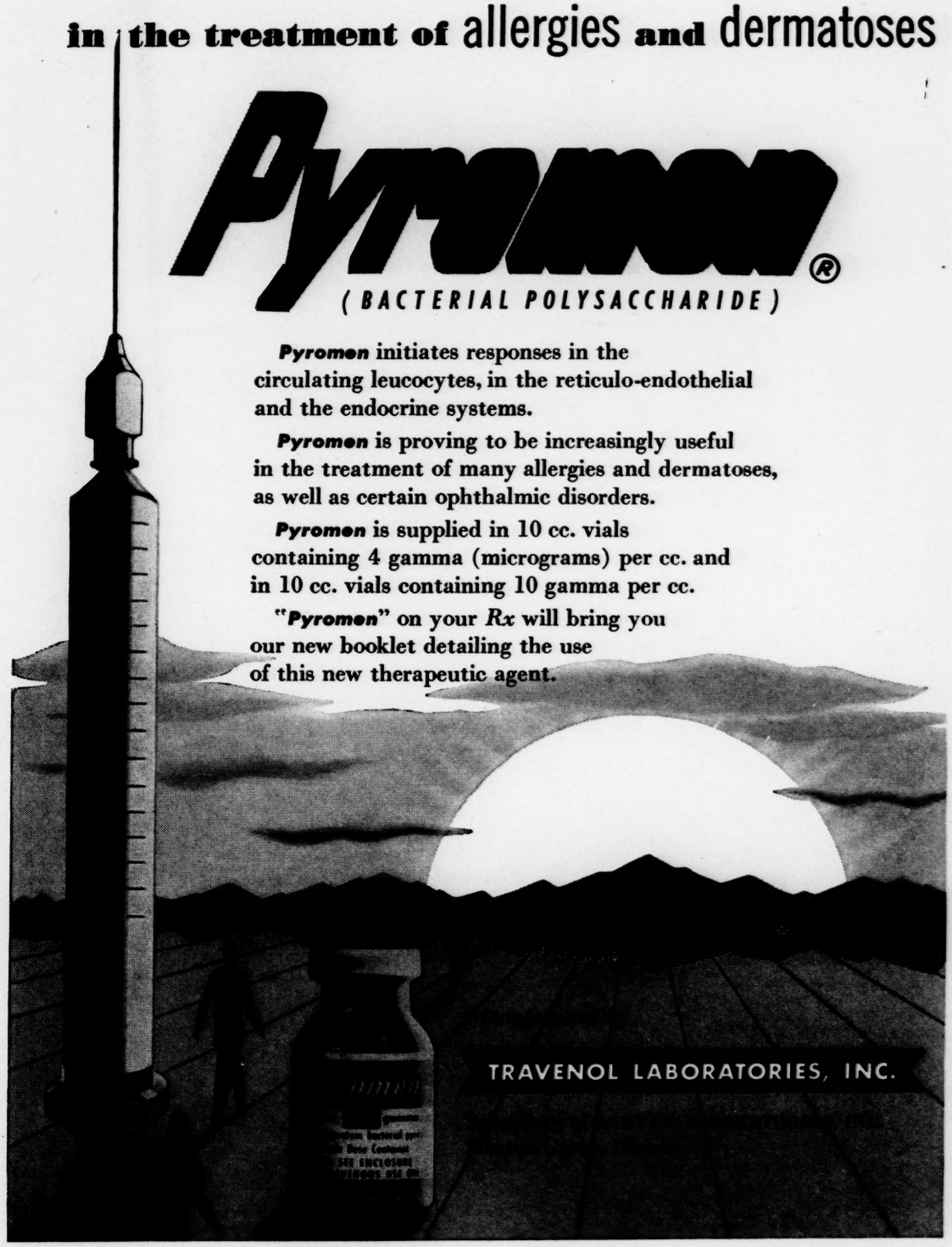
(BACTERIAL POLYSACCHARIDE)

Pyromen **initiates responses in the circulating leucocytes, in the reticulo-endothelial and the endocrine systems.**

Pyromen **is proving to be increasingly useful in the treatment of many allergies and dermatoses, as well as certain ophthalmic disorders.**

Pyromen **is supplied in 10 cc. vials containing 4 gamma (micrograms) per cc. and in 10 cc. vials containing 10 gamma per cc.**

"*Pyromen*" on your *Rx* will bring you our new booklet detailing the use of this new therapeutic agent.



Cortone®

Ophthalmic Dosage Forms Provide Dramatic Benefit in Inflammatory Eye Disease

SUPERFICIAL KERATITIS

Pretreatment

After 3 days' treatment

CORTONE instilled topically every ½ hour during the day and every two hours at night.

Topical Therapy Proves Effective, Convenient, and Economical

In a recent study,[1] CORTONE applied topically, afforded best results in the treatment of lesions of the anterior segment where the response, at times, was phenomenal. The authors recommended that CORTONE be administered locally, when feasible, because of the simplicity of the method, lack of irritation, and absence of undesirable physiological side effects. Other workers[2] noted, "Local therapy . . . reduces the cost to the individual patient . . ."

1. Scheie, H. G., Tyner, G. S., Buesseler, J. A., and Alfano, J. E., *J. A. M. A. Arch. Ophth.* 45:301, March 1951.

2. Leopold, I. H., Purnell, J. E., Cannon, E. J., Steinmetz, C. G., and McDonald, P. R., *Am. J. Ophth.* 34:361, March 1951.

Literature on request

Cortone®
ACETATE
(CORTISONE Acetate Merck)

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY
In Canada: MERCK & CO. Limited—Montreal

the natural

formula:

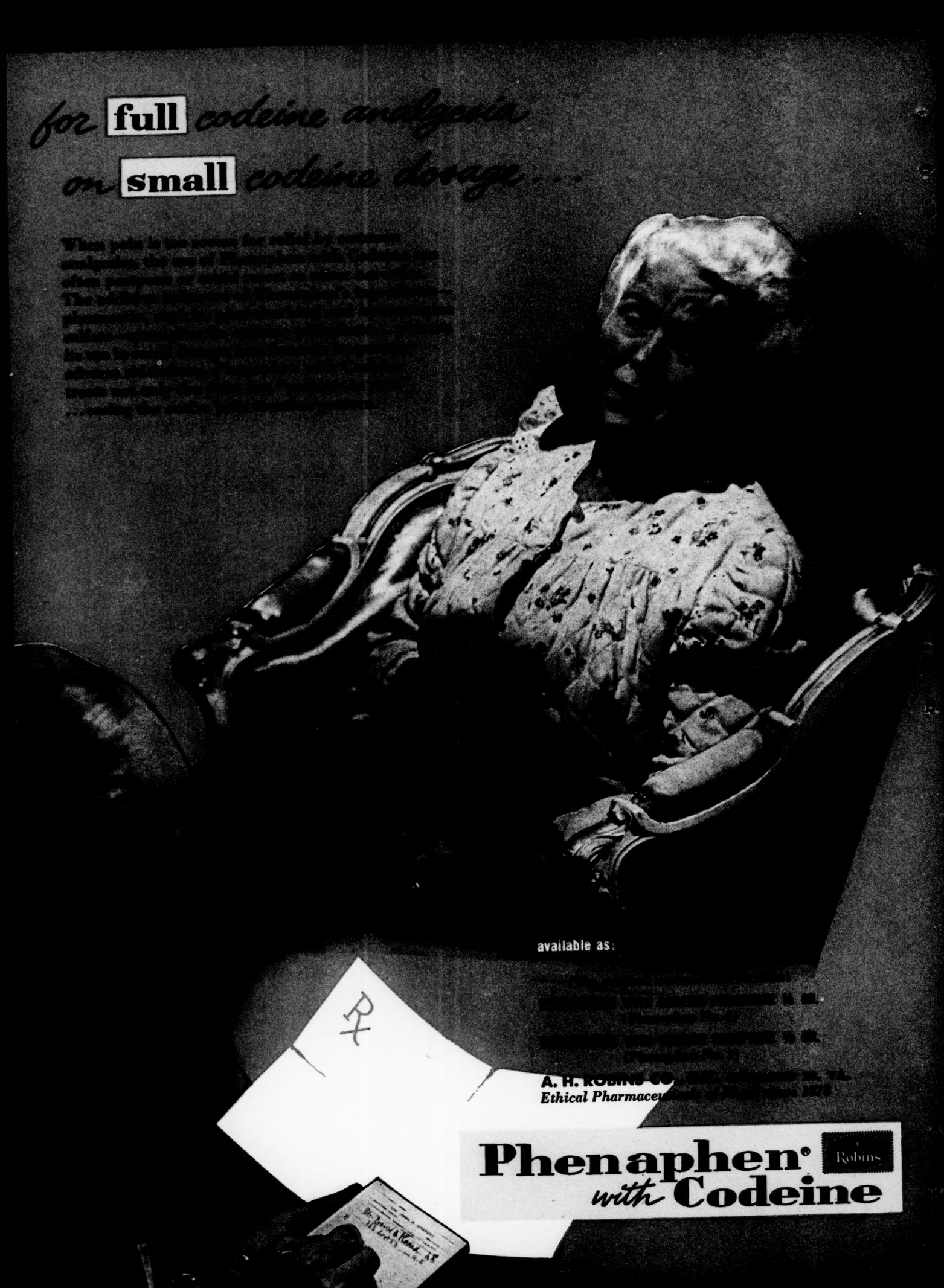
Each tablet or capsule and each 5 cc. of elixir contains hyoscyamine sulfate, 0.1037 mg., atropine sulfate, 0.0194 mg., hyoscine hydrobromide, 0.0065 mg., phenobarbital (1/4 gr.) 16.2 mg.

A. H. ROBINS CO., INC.
RICHMOND 20, VA.
Ethical Pharmaceuticals of Merit since 1878

Prescribed by many doctors,
from any other combination

for **full** *codeine analgesia*

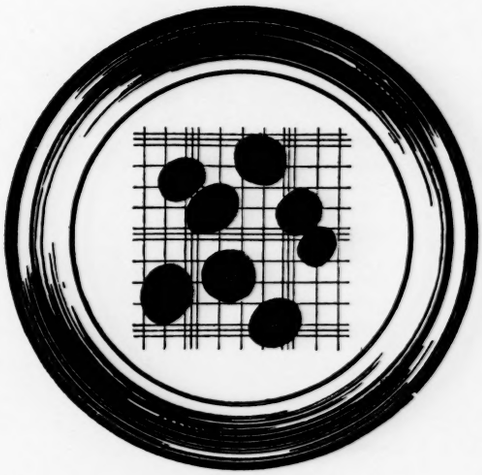
or **small** *codeine dosage . . .*



available as:

A. H. ROBINS CO.
Ethical Pharmaceu

Phenaphen® Robins
***with* Codeine**



more than specific therapy...

may be needed to accelerate recovery in the common anemias.

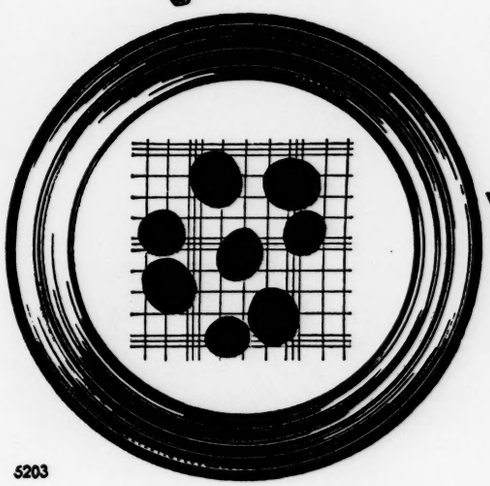
In treating microcytic hypochromic anemia, particularly in the patient of reproductive age or when blood loss of any type is a conditioning factor, you will want to prescribe **not only iron but also all the elements known to be essential for the development and maturation of red blood cells.** "Bemotinic" provides all these factors.

Each capsule contains:		
Ferrous sulfate exsic. (3 gr.)	200.0	mg.
Vitamin B_{12} U.S.P. (crystalline)	10.0	mcg.
Gastric mucosa (dried)	100.0	mg.
Desiccated liver substance, N.F.	100.0	mg.
Folic acid	0.67	mg.
Thiamine HCl (B_1)	10.0	mg.
Vitamin C (ascorbic acid)	50.0	mg.

In macrocytic hyperchromic anemias, the elements contained in "Bemotinic" will provide additional support to specific therapy, or may be used for maintenance once remission has been achieved. In many pernicious anemia patients there is need for iron because of a co-existent iron deficiency.

Suggested Dosage: One or two capsules (preferably taken after meals) three times daily, or as indicated.

No. 340—Supplied in bottles of 100 and 1,000



"Bemotinic"

CAPSULES

for just the right shade of red

Ayerst, McKenna & Harrison Limited
New York, N.Y. • Montreal, Canada

5203

The *weight reduction problem*

a more complete solution . . .

OBEDRIN plus* THE 60-10-70 DIET

Obedrin Tablets permit full utilization of the appetite depressing action of methamphetamine hydrochloride but eliminate the central nervous stimulation, so the patient does not suffer from nervous irritability and insomnia.

The 60-10-70 Basic diet provides the basic minimum of proteins to maintain nitrogen balance, the basic minimum of carbohydrates to "burn off" excessive fat in storage.

Obedrin Tablets and the 60-10-70 basic diet will permit loss of weight with minimum discomfort, thus inviting patient cooperation.

FORMULA

*Semoxydrine Hydrochloride	5 mg.
Pentobarbital Sodium	20 mg.
Ascorbic Acid	100 mg.
Thiamine Hydrochloride	0.5 mg.
Riboflavin	1 mg.
Niacinamide	5 mg.

*Methamphetamine Hydrochloride

Obedrin is supplied in bottles of 100, 500 and 1,000 yellow grooved tablets.

A COMPLIMENTARY PAD OF DIET SHEETS AND A TRIAL SUPPLY OF OBEDRIN SENT TO PHYSICIANS ON REQUEST.

Obedrin

MASSENGILL BRISTOL, TENNESSEE

76.6% of patients preferred

EURAX® CREAM...

76.6%

for relief of pruritus

In a recent study[1] of 200 cases of itching dermatoses, 76.6% of all patients who had had previous experience with other antipruritics expressed a preference for EURAX Cream.

In this study, as in previous reports[2-5], EURAX Cream produced complete relief of itching in approximately 65 per cent of cases, and partial relief in most of the remainder.

Other favorable features of EURAX Cream that were again confirmed include:

- ✓ ***Prolonged effect lasting up to 8 hours or more.***
- ✓ ***No loss of effect on continued use.***
- ✓ ***Virtually complete lack of sensitizing or toxic properties.***

EURAX... not an antihistaminic or a -caine derivative . . . is indicated for prompt, prolonged relief of itch in practically all forms of dermatosis including pruritus due to administration of antibiotics.

EURAX Cream* (brand of crotamiton cream) contains 10% N-ethyl-o-crotonotoluide in a vanishing-cream base.
Tubes of 20 Gm. and 60 Gm. and jars of 1 lb. at your local pharmacy.

Bibliography

1. Hitch, J. M.: North Carolina M. J. *12*:548, 1951.
2. Peek, S. M., and Michelfelder, T. J.: New York State J. Med. *50*:1934, 1950.
3. Couperus, M.: J. Invest. Dermat. *13*:35, 1949.
4. Soifer, A.: Quart. Rev. Int. Med. & Dermat. *8*:1, 1951.
5. Johnson, S. M., and Bringe, J. W.: Arch. Dermat. & Syph. *63*:768, 1951.

*U.S. Pat. #2,505,681.

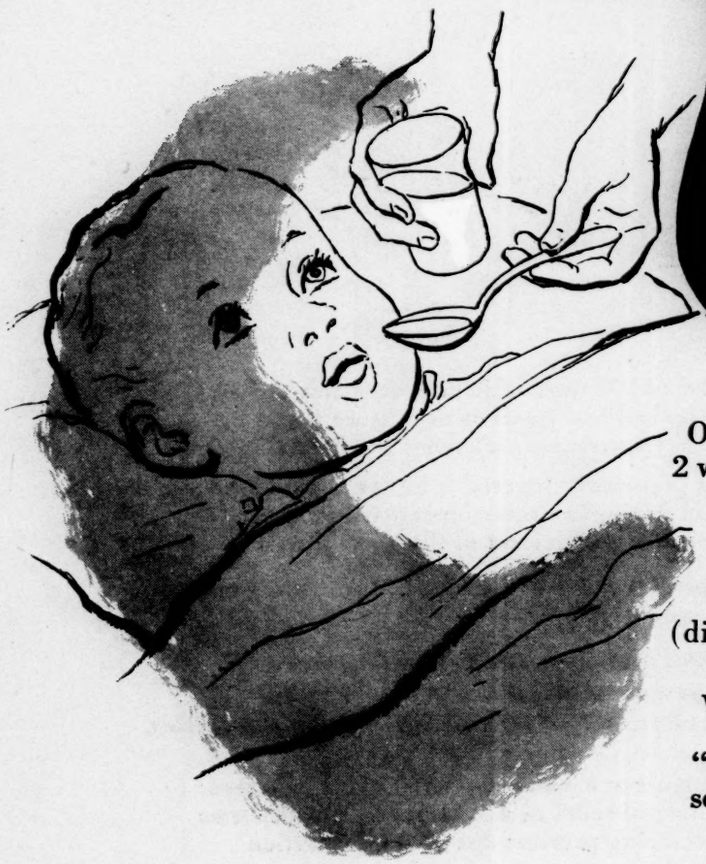
Samples and Reprints on Request

GEIGY PHARMACEUTICALS
Division of Geigy Co., Inc.
220 Church St., New York 13, N. Y.

E-5

citrus is virtually

NON-ALLERGENIC



TYPICAL PATCH TEST

Over 400 infants and children from 2 weeks to 6 years of age acted as test subjects to check the incidence of sensitivity to orange juice. After 2 to 12 months' observation,* "no disturbance of bowel function (diarrhea or constipation) that could be attributed to the orange juice" was found. Also, the occurrence of regurgitation and rashes was "minimal". In the rare instances of sensitivity, care exercised by gentle reaming of juice (or the use of frozen concentrate) to avoid contamination with peel oil usually obviates the difficulty.

**J. Pediat. 39:325, 1951*

FLORIDA CITRUS COMMISSION • LAKELAND, FLORIDA

FLORIDA *Citrus*

ORANGES • GRAPEFRUIT • TANGERINES

The newest approach to the management of *atherosclerosis* and the treatment of *angina pectoris*

REQUIRES NO HOSPITALIZATION

atherosclerosis

It has been found[1] that non-recurrence of myocardial infarction is associated with a dietary reduction in the blood level of the large lipoprotein molecules as determined by ultracentrifugal flotation analysis.[2] Elevated levels of these large lipoprotein molecules reflect a fundamental metabolic defect intimately related to the causation of atherosclerosis.[1]

Heparin[3] profoundly influences blood lipid transport in the human through a facilitation of the handling of fat. In this way, the use of heparin returns the level of serum lipoproteins toward the normal pattern.

angina pectoris

The changes produced by heparin in the level of lipoprotein molecules away from the atherosclerosis toward the normal pattern are paralleled by a genuine relief of angina pectoris. Doses of 25 to 100 mg. of heparin once or twice a week will give lasting relief independently of any anticoagulant or vasodilator action.[1]

HED*-HEPARIN

HEPARIN SODIUM INJECTION U.S.P.
10 cc. vials 1000 and 5000 U.S.P. Units per cc.

is a reliable product admirably suited in these newest heparin applications in addition to its use as an anticoagulant. Neither hospitalization of patient, nor clotting time determinations are required, because of the small dosages of HED-HEPARIN needed in the management of Atherosclerosis and treatment of Angina Pectoris.

1. Jones, H. B., Gofman, J. W., Lindgren, F. T., Lyon, T. P., Graham, D. M., Strisower, B. and Nichols, A. V.: Lipoproteins in Atherosclerosis, Am. J. Med., 11:358-380 (Sept.) 1951.

2. Lyon, T. P., Jones, H. B., Graham, D. M., Gofman, J. W., Lindgren, F. T. and Yankley, A.: Further Studies on the Relationships of Sf 10-20 Lipoprotein Molecules to Atherosclerosis, Int. Med. Sect. A.M.A. Meet., Atlantic City (June 13) 1951.

3. Graham, D. M., Lyon, T. P., Gofman, J. W., Jones, H. B., Yankley, A., Simonton, J. and White, S.: Blood Lipids and Human Atherosclerosis II, The Influence of Heparin on Lipoprotein Metabolism, Circulation, IV:666 (Nov.) 1951.

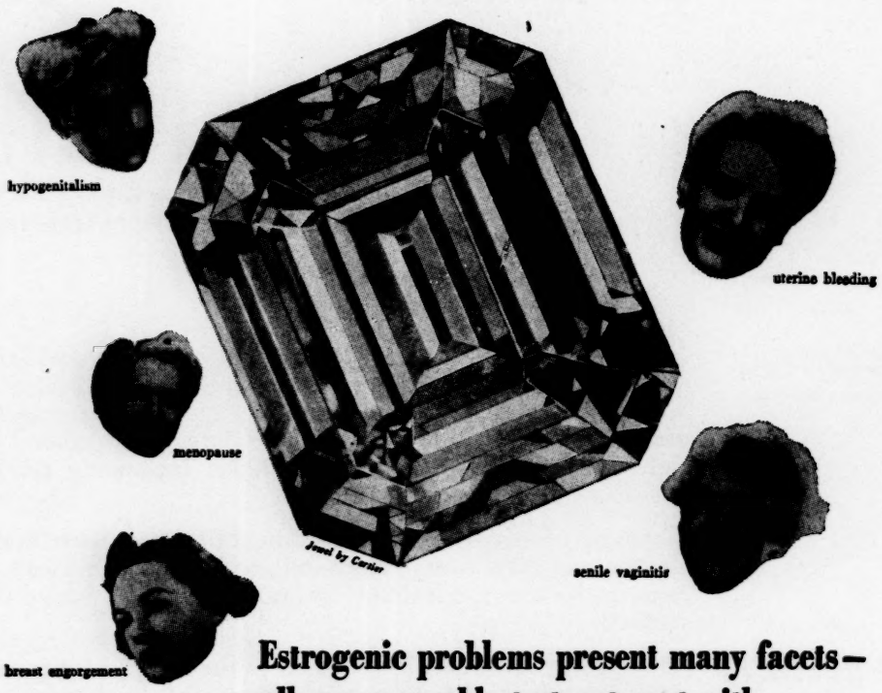
*T.M.

HED Pharmaceuticals, Inc.

H. E. Dubin, President

NEW ROCHELLE • NEW YORK

"No Compromise with Quality"



Estrogenic problems present many facets— all are amenable to treatment with...

BENZESTROL

2,4 di(p-hydroxyphenyl)-3-ethyl hexane

– the multi-faceted synthetic estrogen is:

CLINICALLY EFFECTIVE: Prolonged beneficial effects are obtainable with BENZESTROL. BENZESTROL is effective orally, whereas natural estrogens lose a large proportion of activity when administered by mouth.

CLINICALLY ECONOMICAL: Therapeutically comparable doses of BENZESTROL are much less expensive than natural estrogens.

NON-TOXIC: Clinical studies have proved that BENZESTROL when administered in therapeutically effective doses, is singularly free from undesirable, toxic, side reactions[1-6] . . . as exhibited with some other synthetics.

supplied

ORAL — TABLETS
0.5 mg. (white) 100's and 1,000's
1.0 mg. (grey) 100's and 1,000's
2.0 mg. (orange) 50's, 100's & 1,000's
5.0 mg. (pink) 50's, 100's & 1,000's

TABLETS *w/ Phenobarbital**
(yellow)
1 mg. Benzestrol with 15 mg. (¼ gr.) phenobarbital 100's

ELIXIR
25 mg. per fl. oz. Pint bottles

INTRAMUSCULAR
SOLUTION in OIL
5 mg. per cc. 10 cc. vials

AQUEOUS SUSPENSION
(Contains 2% benzyl alcohol)
5 mg. per cc. 10 cc. vials

LOCAL —VAGINAL TABLETS
0.5 mg. 100's

*When yet council accepted.

AVERAGE DOSE: Menopause — 2 to 3 mg. daily, orally; or ½ to 1 cc. parenterally, every 3 to 5 days.

Control of Breast engorgement—5 mg. orally, 3 or 4 times for 5 to 6 days.

Generous 2 mg. oral professional samples and complete literature on request.

References: 1. Bulford, A.R.: J.A.M.A. 125:689 (1944)
2. Talesnik, M.R.: Amer. Jrl. Obst. & Gyn. 46:346 (1943)

Schieffelin & Co. / Since 1794
Pharmaceutical and Research Laboratories
19 Cooper Square, New York 3, N. Y.

a statement on

RIMIFON

the new Roche antituberculous drug

The studies published in the current issues of the American Review of Tuberculosis, Diseases of the Chest and the Sea View Bulletin indicate that Rimifon* (isonicotinic acid hydrazide) is a potent antituberculous agent.

Numerous additional investigations are now under way to obtain further information as to optimal dosage, duration of treatment and incidence and significance of side reactions. The medical profession will be kept informed by means of letters and announcements in medical journals.

At present, Rimifon is available for clinical investigation only but supplies for prescription and hospital use will be available in the near future.

*Trade Mark

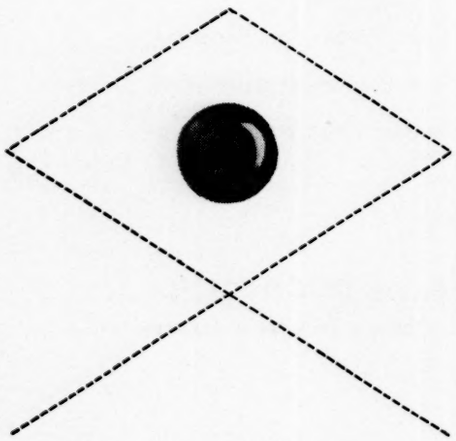
HOFFMANN-LA ROCHE INC.
Roche Park • Nutley 10 • New Jersey

MI-CEBRIN

(VITAMIN-MINERAL SUPPLEMENTS, LILLY)

provides all essential vitamins

and those trace elements believed to be indispensable — for normal, healthy existence, continued vigor, efficiency.



Your prescription for one tablet 'Mi-Cebrin' daily assures the following intake:

Thiamine Mononitrate	10	mg.
Riboflavin	5	mg.
Pyridoxine Hydrochloride	2	mg.
Pantothenic Acid (as Calcium Pantothenate)	10	mg.
Nicotinamide	30	mg.
Vitamin B_{12} (Activity Equivalent)	3	mcg.
Folic Acid	0.1	mg.
Ascorbic Acid (as Sodium Ascorbate)	100	mg.
Alphatocopherols	5	mg.
Vitamin A 10,000 U.S.P. or International units		
Vitamin D 1,000 U.S.P. or International units		

and also furnishes (approximate amounts):

Iron (as Ferrous Sulfate)	15	mg.
Copper (as the Sulfate)	1	mg.
Iodine (as Potassium Iodide)	0.15	mg.
Cobalt (as the Sulfate)	0.1	mg.
Boron (as Boric Acid)	0.1	mg.
Manganese (as the Glycerophosphate)	1	mg.
Magnesium (as the Oxide)	5	mg.
Molybdenum (as Ammonium Molybdate)	0.2	mg.
Potassium (as the Chloride)	5	mg.
Zinc (as the Chloride)	1.5	mg.

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

The American Journal of Medicine

VOL. XII APRIL, 1952 No. 4

Editorial

The Lipid Transport Functions of the Plasma

THE recent intense interest of physicians in the study of plasma lipids may be traced on the one hand to the introduction of new technics and on the other to the growing evidence that abnormal concentrations of lipids in the plasma are related in some way to the pathogenesis of arteriosclerosis.

The transport of lipids in the blood unquestionably serves many and diverse body functions. The most commonplace, and the one frequently ignored in the recent emphasis upon the relationship of cholesterol to the pathogenesis of arteriosclerosis, is the transport of lipids for body energy. In terms of the weight of lipid material transported this is by all odds the most important function. The transport of fat in an aqueous medium like the blood encounters the difficulties of insolubility of neutral fat and the toxicity of fatty acids and soaps free in the plasma. Some of these difficulties seem to have been solved by the incorporation of fatty acids into phospholipids and cholesterol ester, and by the association in some fashion of neutral fat and perhaps fatty acids with proteins. The different lipoproteins of the plasma have yet to be fully described either as to structure or function. We wish in this communication to comment upon the efforts of our New Orleans group at differentiation and description of lipid complexes in the serum, with particular reference to the beginning of a hypothesis of transport of energy lipids.[1,2]

The mechanisms of transport of energy lipids may have similarities to the transport of oxygen and carbon dioxide. The movement of these gases in the plasma is greatly limited due to the formation of bubbles if an excess is introduced. The study of transport of oxygen and carbon dioxide by the hemoglobin was greatly facilitated by discovery of the change in optical properties of hemoglobin associated with loading and unloading. In like fashion it may turn out that unraveling the mechanisms of lipid transport by proteins may be greatly aided by detection and measurement of a change in the physical characteristics of the lipoprotein complex as a lipid burden is taken on or discharged.

The study of physiology of serum lipids in New Orleans is an outgrowth of refinement in the technic of using the quantity ultracentrifuge, with avoidance of pretreatment of serum, a fortunate choice of centrifugal force, rotor geometry and time of centrifugation, and the use of extensive chemical analyses to measure the redistribution of lipids and proteins effected by the differentiating force.[1] Each of the four lipid components estimated, free cholesterol, cholesterol ester, phospholipids and neutral fat, was found to have a distinctive and reproducible arrangement in the column of centrifugate of normal subjects, and the proportion of lipid phosphorus tagged by P^{32} in a given time period following administration of isotope likewise showed a distinctive pattern.[2]

Chemical analyses of centrifugates of normal sera and mathematical studies of the results show the presence in normal serum of at least three groups or systems of lipid complexes: (1)

[1] TURNER, R. H., SNAVELY, J. R., GOLDWATER, W. H., RANDOLPH, M. L., SPRAGUE, C. C. and UNGLAUB, W. G. The study of serum proteins and lipids with the aid of the quantity ultracentrifuge. I. Procedure and principal features of the centrifugate of untreated normal serum as determined by quantitative analysis of samples from ten levels. *J. Clin. Investigation*, 30: 1071–1081, 1951.

[2] TURNER, R. H. Serum proteins and lipids. Tenth Conference on Liver Injury of the Josiah Macy, Jr. Foundation. (In press.)

Those of most elaborate lipid constitution contain all four of the lipid components measured, three of which at all levels are interrelated in mathematical fashion, but neutral fat, the fourth component, was found to have stoichiometric relationships only in one part of the column, the cream layer. These complexes contain all of the free cholesterol and are concentrated in two portions of the column, the cream layer (minimum density), at the top and in a broad mid-zone (medium density). Radioactive phosphorus is rapidly incorporated into the complexes of lowest density and slowly into those of medium density. (2) Lipoproteins which contain phospholipid but not free cholesterol are found at all levels in the column. Phospholipids and neutral fat are the only lipids found toward the bottom of the column with the usual technic of centrifugation and likewise in the zone of minimum concentration just below the cream layer after prolonged centrifugation. Radioactive phosphorus is taken into these complexes rapidly and according to repeatable pattern. (3) Cholesterol ester-containing lipoproteins which do not contain free cholesterol are found in two concentrations. It is not assumed that any one of these three systems of lipid complexes is entirely homogeneous. Because the fatty acids of either phospholipids or cholesterol esters are found in all three systems, all may play important roles in energy metabolism.

There are two questions of extreme importance in the formulation of hypotheses of lipid transport. First, do the lipoproteins function as lipid carriers in the same sense that hemoglobin is the carrier for oxygen and carbon dioxide? The utilization of the same molecule of protein over and over again for many loadings and unloadings offers great economy in body metabolism in contrast to the notion that a lipoprotein with its lipid load is synthesized as a complete entity and undergoes catabolism of both lipid and protein portions simultaneously when the transport of a single lipid load has been completed. The role of a protein in a mechanism of the second sort could hardly be called that of carrier.

Second, what changes are there in the characteristics of a lipid carrier which are associated with loading and unloading and which might be useful in describing the mechanisms of lipid transport? We have evidence that change in density of lipoprotein complexes associated with and perhaps due to loading and unloading by lipids, especially fat, occurs and should be useful in the analysis of the mechanisms of lipid transport. Direct evidence was obtained by the study of whole serum delipidated by repeated quick-freezing in the presence of ether. Such delipidated serum was found to have lost only a small portion of its phospholipids but practically all of the other lipids. The distribution of lipid phosphorus in the column of centrifugate was radically changed by the procedure. Phospholipid concentration fell to zero in the centrifugate of lowest density, was diminished slightly in the medium density zones and increased markedly toward the bottom of the column, indicating that removal of lipids other than phospholipids changed the sedimentation characteristics of the phospholipid-containing protein, increase in density resulting from removal of low density lipid components.

The study of alimentary lipemia, starvation lipemia and acute hepatitis with hyperlipemic serum brought out indirect evidence that an extra load of lipids caused such a deviation from normal lipid distribution as to support the general concept that loaded complexes are less dense than unloaded ones. In centrifugates of hyperlipemic hepatitis serum there is a remarkable sparsity of lipids, especially phospholipids, in the lower denser half of the column, and an excess in the upper half and it is in the upper half where the hyperconcentration of lipids other than phospholipid is found. The distribution of lipids peculiar to centrifugates of hepatitis serum is in some respects the reverse of that of delipidated normal serum. There is a similar trend when lipemia results from starvation or ingesting a high fat meal. In these three conditions the transport of fat places an extra burden on the lipid transport mechanism. It seems not unlikely that these peculiarities in distribution may be expressions of a common mechanism, namely, that loading of certain phospholipid-containing lipoproteins by low density fat has so changed their sedimentation characteristics, particularly density, that these loaded complexes localize at a higher level in the column where the centrifugate is less dense.

A third line of evidence depends upon the degree and sequence of incorporation of P^{32} into

the phospholipids at different levels of the centrifugate. Findings with this technic suggest that two principal streams of newly synthesized phospholipids enter the plasma, one in high and medium density lipoproteins which contain no free cholesterol and the other in minimum density complexes which contain both sorts of cholesterol and a large proportion of neutral fat. From day to day in a given subject there were changes in distribution of isotope in the centrifugate which suggested that changes in density of the lipoproteins of the first group occurred after they first appeared in the blood stream, which may have been caused by loading with fat. Gofman and his associates have suggested transformation of lipid complexes of minimum density into those of increased density.[3]

According to our hypothesis, at least two of the three systems of lipoproteins, the two which contain phospholipids, may in a strict sense act as carriers for fat and that change in physical characteristics, especially density, occurs with loading and unloading. It seems likely that the fat handled by each of these two systems may have different origins and destinations.

ROY H. TURNER, M.D.

[3] JONES, H. B., GOFMAN, J. W., LINDGREN, F. T., LYON, T. P., GRAHAM, D. M., STRISOWER, B. and NICHOLS, A. V. Lipoproteins in atherosclerosis. *Am. J. Med.*, 11: 358, 1951.

Clinical Studies

Cerebral Circulation and Metabolism in Chronic Pulmonary Emphysema*

With Observations on the Effects of Inhalation of Oxygen

JOHN L. PATTERSON, JR., M.D., ALBERT HEYMAN, M.D. *and* T. WHATLEY DUKE, M.D.
Atlanta, Georgia

REDUCTION in arterial oxygen tension or elevation of carbon dioxide tension, produced by altering the composition of the inspired air, have been shown to exert dilator effects upon the cerebral blood vessels in man and to cause an increase in cerebral blood flow.[1] Similar changes in blood gas tensions commonly develop in chronic pulmonary emphysema as the disease process advances.[2] Efforts to overcome the anoxemia in these patients by the administration of oxygen have been reported to result in untoward reactions[3, 5] in approximately 10 per cent of cases.[6] These reactions have included convulsive seizures, drowsiness, stupor, coma and, in rare instances, death.

There would appear therefore to be sound reasons for anticipating abnormalities in the cerebral circulation in patients with chronic pulmonary emphysema. This report presents our findings in nine such patients and in eight control subjects in whom the cerebral circulation and metabolism were studied both before and during administration of 85 to 100 per cent oxygen. Observations on the changes in spinal fluid pressure and pulmonary ventilation with oxygen inhalation are also presented.

PATIENT MATERIAL AND METHODS

The nine patients in this study had a mean age of fifty years. They all gave a history of previous respiratory infections, chronic cough and exertional dyspnea of varying severity. Four of them had asthma of many years' duration. On physical examination the patients showed kyphosis, an increase in anteroposterior diameter of the thoracic cage and a limited range of respiratory excursions. Two of them had clubbing of the fingers and six showed cyanosis of the nail beds, ears or mucosal surfaces. Roentgenograms of the chest showed signs of pulmonary emphysema with decreased density of lung fields, wide intercostal spaces and flattened diaphragms. Moderate or extensive degrees of pulmonary fibrosis were noted in four individuals. Seven patients had evidence of cor pulmonale with cardiac enlargement and dilatation of pulmonary arteries on x-ray examination. Five of these seven patients had evidence of congestive failure and the majority showed electrocardiographic evidence of right ventricular enlargement. In two individuals (C. G. and C. M.) the pulmonary arterial pressures, determined by cardiac catheterization, within a few days of the cerebral studies were 13 and 60 mm. Hg, respectively. Although the pulmonary arterial pressure in C. G. was normal, his pulmonary arterial-pulmonary capillary pressure gradient was 16 mm. Hg, as compared with the normal mean in this laboratory of 6.7 mm. Hg. The cardiac indices (T-1824 dye) in C. G. and C. M. were 2.6 and 3.3 L./minute, respectively.

Eight patients, convalescing from such operations as herniorrhaphy and from various illnesses such as gonorrheal arthritis, dermatitis and peptic ulcer, were used as control subjects. These patients had no evidence of intracranial or pulmonary complications. The mean values in these control subjects for cerebral blood flow, oxygen consumption and vascular resistance when they were breathing room air agreed very

* From the Departments of Physiology and Medicine, Emory University School of Medicine and the Medical Service of Grady Memorial Hospital, Atlanta, Ga. This investigation was supported in part by a research grant from the National Institutes of Health, U. S. Public Health Service, and in part by Contract N9onr92500, Office of Naval Research, Project Designation No. NR 112-607.

closely with those of a larger group of fourteen control subjects who were not studied during oxygen administration.

The cerebral blood flow (CBF) was measured by the nitrous oxide technic of Kety and Schmidt,[7] with the minor modifications previously described.[8] The cerebral oxygen consumption ($CMRO_2$) was calculated from the CBF and the cerebral arteriovenous oxygen difference. The cerebral vascular resistance (CVR) was calculated from the CBF and the mean arterial pressure, measured directly from the femoral artery with a damped mercury manometer. Control observations of the cerebral circulation were performed with the patient breathing 21 per cent oxygen, 15 per cent nitrous oxide and 64 per cent nitrogen. Ten minutes later the subject was given 100 per cent oxygen by face mask for a period of twenty minutes. At the end of this time the gas was changed to 85 per cent O_2, 15 per cent N_2O and a second blood flow determination carried out.

Arterial and venous blood samples were drawn just before and at the end of each blood flow procedure. These samples were pooled and their oxygen and carbon dioxide content was measured by the combined procedure for these gases described by Peters and Van Slyke,[9] with modifications required by the presence of nitrous oxide, as suggested by Kety and Schmidt. The nitrous oxide content of blood samples was determined by the manometric method of Orcutt and Waters[10] as modified by Kety and Schmidt. Oxygen capacity of blood was obtained by equilibrating the sample with air in a small flask, analyzing for oxygen manometrically and making the usual correction for dissolved oxygen. Hemoglobin concentration was calcus lated from the oxygen capacity. Arterial pH wameasured with the glass electrode of a Cambridge Model R.pH meter, with corrections for room temperature and instrument error. Arterial pCO_2 was calculated from the pH, CO_2 content and hematocrit, by means of the nomogram of Singer and Hastings.[11] Arterial pO_2 was calculated from the pH and the per cent oxyhemoglobin saturation, using the dissociation curves of Dill.[12]

The pulmonary ventilation was measured during inhalation of both 100 per cent O_2 and 21 per cent O_2, 79 per cent N_2 by means of a demand regulator and Tissot spirometer, and corrected to BTPS (body temperature, ambient pressure, saturated with water vapor). Spinal fluid pressures were measured by means of a water manometer with the patient in the right lateral decubitus position. The pressures were followed with the patient breathing room air through a mask and during inhalation of 100 per cent oxygen.

RESULTS

There was an evident tendency for the cerebral blood flow to be higher in the patients with emphysema than in the control subjects. (Table 1 and Fig. 1.) The mean CBF value was 68 cc. in the emphysematous patients ($.02 > p > .01$) compared with 50 cc./100 gm. brain/minute in the control subjects. Only two of the patients with emphysema had CBF values below the normal mean. (Fig. 1.) Since the mean arterial pressure in the patients with emphysema was normal, the mean cerebral vascular resistance was somewhat below that of the control subjects although not significantly so ($.6 > p > 5$).

During the inhalation of 85 to 100 per cent oxygen the mean cerebral blood flow in patients with emphysema rose from 68 to 79 cc./100 gm./minute ($.4 > p > .3$). In contrast, the control subjects showed a decrease in CBF from a mean value of 50 cc. to 44 cc./100 gm./minute. A reduction in CBF during oxygen inhalation occurred in only two patients with emphysema, both of whom had initially low CBF values. The mean value for CBF in the emphysematous patients during inhalation of oxygen was significantly ($p < .01$) different from that found in the control subjects during the same period.

The arterial pressure in both groups of patients was altered very little by oxygen. In general, the CVR in the patients with emphysema was reduced slightly by oxygen administration.

The mean cerebral oxygen consumption in the patients with emphysema was slightly less than the control average. Oxygen inhalation did not produce a change in the mean $CMRO_2$ in either the patients with emphysema or in the control subjects. Mental changes developed in only one patient (C. M.) during the oxygen period. This individual was moderately confused while breathing air and became irrational and combative while breathing oxygen. Three hours later he became rational but had amnesia for the events of the earlier period. The $CMRO_2$ in this patient while he was breathing oxygen was considerably higher than the baseline value.

TABLE 1

CEREBRAL FUNCTIONS AND BLOOD CONSTITUENTS IN EMPHYSEMATOUS PATIENTS AND IN CONTROL SUBJECTS

Patient	Age	CBF cc./100 gm./min.		$CMRO_2$ cc./100 gm./min.		CVR mm. Hg/ cc./100 gm./min.		Mean Art. Pressure (mm. Hg)		A-V Oxygen (vol. %)		Hemoglobin (gm./100 cc.)	Art. HbO_2 Saturation (%)		Art. O_2 Cont. (vol. %)		Art. CO_2 Cont. (vol. %)		Art. pH		Art. pCO_2 (mm. Hg)		Art. pO_2* (mm. Hg)	Remarks
		Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2		Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	
J. B.	54	35	30	2.8	2.8	3.0	3.5	103	106	8.0	9.2	16.7	81	95	18.4	21.5	53.4	56.0	7.38	7.24	50	70	48	Asthma 46 years; chest markedly emphysematous; cor pulmonale
I. H.	28	42	30	4.1	3.0	2.3	3.0	95	90	9.8	9.9	17.4	82	100	19.3	23.4	53.9	53.5	7.34	7.32	54	56	50	Asthma 17 years; cor pulmonale; cyanosis and clubbing of fingers; moderate fibrosis of lungs
E. D.	53	61	73	2.1	2.8	1.8	1.4	108	103	3.4	3.9	11.3	60	75	9.3	11.5	49.2	50.3	7.42	7.34	39	47	30	Resolving pneumonitis, chronic pulmonary infection and fibrosis; cor pulmonale; ? early failure
M. K.	48	64	82	2.7	2.9	1.3	1.1	85	88	4.1	3.5	14.7	66	98	13.2	19.6	63.1	65.8	7.41	7.36	56	62	34	Respiratory disease since childhood; extensive fibrosis; cyanosis; cor pulmonale; congestive failure
R. A.	59	64	97	3.3	2.9	1.3	0.8	84	80	5.1	3.0	16.0	73	98	15.7	21.0	62.6	67.7	7.41	7.16	57	86	37	Asthma 8 years; cor pulmonale; died 2 weeks later with congestive failure
C. G.	59	71	86	2.8	2.8	1.0	0.8	73	72	4.0	3.2	14.1	78	95	14.9	18.0	54.5	55.4	7.30	7.16	57	77	47	Bronchiectasis; pulmonary fibrosis; cyanosis; marked progressive cough 10 years' duration
T. M.	32	85	102	2.4	1.4	1.2	1.0	104	98	2.9	1.4	13.9	60	94	11.3	17.7	61.2	66.4	7.25	7.15	73	96	35	Cor pulmonale; congestive failure 2 years; clubbed fingers; cyanosis
J. J.	59	94	101	2.0	1.9	0.9	0.8	87	82	2.2	1.9	13.2	51	96	9.2	17.1	63.8	65.5	7.34	7.20	62	84	29	Progressive exertional dyspnea 3 years; chest markedly emphysematous
C. M.	56	94	113	2.2	3.7	0.8	0.7	79	84	2.3	3.3	13.1	60	99	10.8	17.6	75.1	76.4	....	....	..	..	..	Asthma 19 years; cor pulmonale; cyanosis; congestive failure
Mean Values	50	68†	79†	2.7	2.7	1.52	1.46	91	89	4.6	4.4	14.6	68	93	13.6	18.6	59.6	63.0	7.36	7.24	58	70	39	
Mean (8 control patients)	32	50	44	3.0	3.2	1.9	2.1	93	91	6.0	7.2	13.4			16.1	17.8	47.6	47.3						

All mean values have been calculated from the data on individual patients.

* The arterial pO_2 during inhalation of oxygen in patient E. D. was 43 mm. Hg. The values in other patients were too high to be read accurately from dissociation curves.

† Denotes statistically significant difference from mean values obtained in control subjects breathing similar compositions of inspired gas.

Changes in the blood gases in the patients with chronic pulmonary emphysema were similar to those which have been reported by others.[2] The mean arterial oxyhemoglobin saturation was 68 per cent, the mean pO_2 39 mm. Hg, the mean pCO_2 58 mm. Hg and the arterial pH 7.36. Inhalation of oxygen raised the arterial oxygen saturation into the range 94 to 100 per cent in all patients except one (E. D.) and produced an increase in the mean pCO_2 to 70 mm. Hg and a reduction in arterial pH to a mean of 7.24. The acidosis and the increase in CO_2 tension and content observed in the emphysematous patients given oxygen are probably related to the depressive effect of oxygen on the pulmonary ventilation. (Fig. 2.) The average ventilations measured in four patients while breathing air for six minutes and oxygen for twelve minutes were 8.8 L./minute and 6.0 L./minute, respectively.

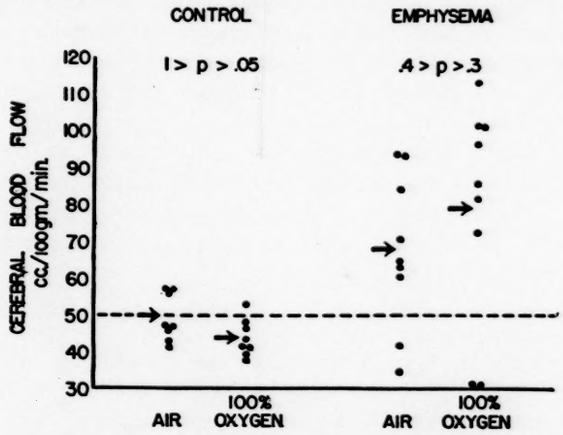


FIG. 1. Distribution of cerebral blood flow values in control subjects and in patients with emphysema during inhalation of air and of oxygen.

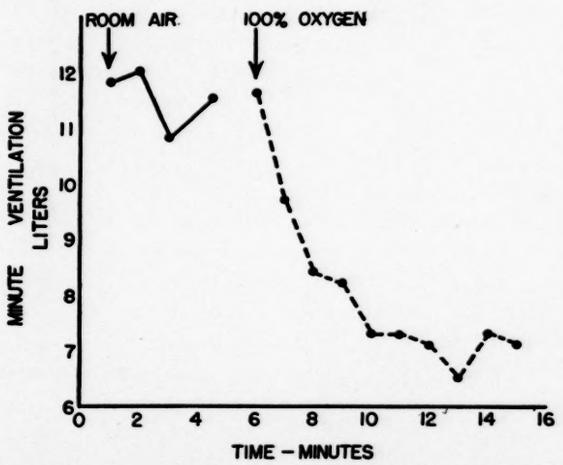


FIG. 2. Response of the pulmonary ventilation to oxygen administration in an elderly patient with severe chronic emphysema. Data on this patient's CBF are not included in this report.

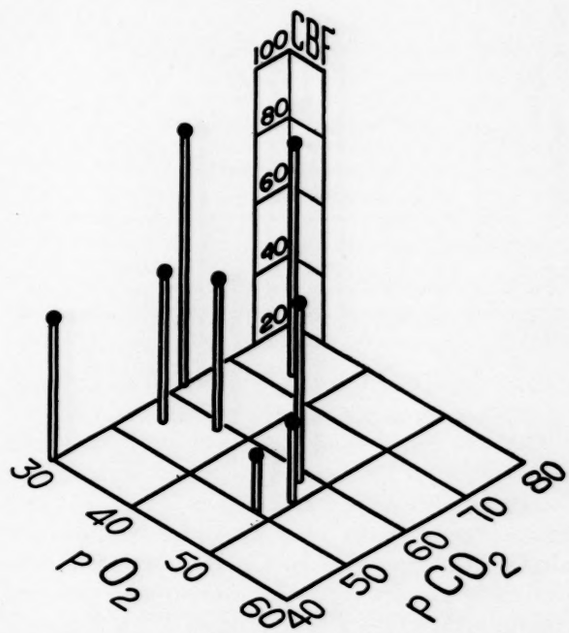


FIG. 3. Three-dimensional chart showing interrelationships between CBF (cc./100 gm./min.), arterial pO_2 (mm. Hg) and arterial pCO_2 (mm. Hg) in eight patients with emphysema breathing air.

The cerebral blood flow in the patients with emphysema while they were breathing room air could be correlated to some extent with the arterial tensions of oxygen and carbon dioxide. The two patients with the lowest CBF determinations had the highest pO_2 and lowest pCO_2 values, while the highest CBF values were found in patients with the lowest pO_2 and the highest pCO_2 levels. (Fig. 3.) The same type of multiple correlation cannot be attempted for the data of the oxygen period, since the arterial oxygen saturation was too high to permit accurate pO_2 readings from the dissociation curves. Six of the eight patients on whom arterial pCO_2 and pH data are available showed a rise in CBF during oxygen administration. In each of these six patients there was an increase in pCO_2 and a decrease in pH, but the magnitude of the changes did not correlate well with the amount of increase in the cerebral blood flow. However, the patient (R. A.) who had the greatest increase in CBF with oxygen also manifested the largest

increase in pCO_2 and decrease in pH. The patient (J. B.) in whom the CBF fell slightly with oxygen had pCO_2 and pH changes similar to those found in the six patients in whom the CBF increased. The one patient (I. H.) who had an appreciable fall in blood flow had almost no change in either pCO_2 or pH.

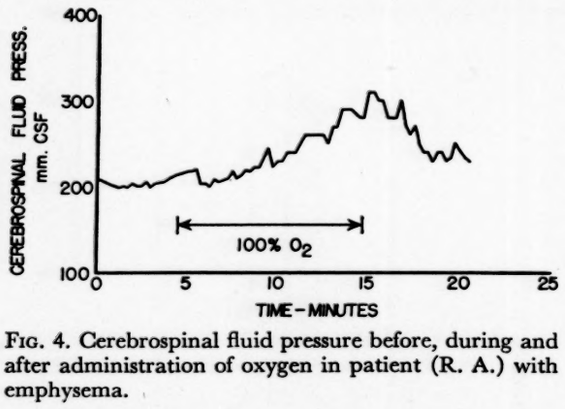


FIG. 4. Cerebrospinal fluid pressure before, during and after administration of oxygen in patient (R. A.) with emphysema.

Cerebrospinal fluid pressure in six patients with emphysema was slightly or moderately increased by oxygen inhalation. (Fig. 4.) The mean pressure with the patients breathing room air was 198 mm. C.S.F. During approximately ten minutes of oxygen inhalation the pressure rose to an average peak value of 279 mm., with an extreme value of 470 mm. C.S.F. In five control subjects with asymptomatic neurosyphilis the cerebrospinal fluid pressure either remained the same or fell slightly during oxygen breathing.

COMMENTS

The elevation of the mean cerebral blood flow in the patients with emphysema when they were breathing air is entirely compatible with the known effects of alteration of the arterial tensions of oxygen and of carbon dioxide. The figures for mean arterial pO_2 and pCO_2 in these patients are seen to be decidedly abnormal when compared with the values of 97.1 mm. Hg and 41.6 mm. Hg, respectively, in healthy young adults.[13] A synergistic effect would be expected from reduction of the pO_2 and elevation of pCO_2. The observed reduction in CVR and increase in CBF were actually considerably smaller than would be predicted on the basis of the effects produced by rapid alterations in the arterial gas tensions.[1] It is possible that the very gradual development of the abnormal tensions in emphysema allowed adaptive changes to take place in the cerebral vessels. A contributory factor may have been the maintenance of a relatively normal arterial pH in these patients through a compensatory increase in plasma bicarbonate. Reduction in arterial pH appears to favor an increase in cerebral blood flow.[1,14]

Apart from changes in the arterial blood the state of the heart itself might have been a factor influencing the cerebral blood flow. The importance of this factor is admittedly difficult to evaluate. It is of interest, however, that there was no tendency for the CBF to be lower in the patients with congestive failure. In other types of heart disease congestive failure tends to be associated with a reduced cerebral blood flow.[15]

The changes in arterial gas tensions and pH with the administration of oxygen evidently are relatively rapid. For some time, at least, the pulmonary ventilation is reduced, with a consequent rise in arterial CO_2 tension. The conventional explanation for the depression of respiration is the withdrawal of the hypoxic stimulus to chemoreceptor mechanisms. The associated fall in pH is most likely due to the combined effects of carbon dioxide retention and the increase in the amount of oxyhemoglobin in the arterial blood. The cerebral blood vessels under these circumstances are subjected to stimuli in competition: the dilator stimulus of an increase in pCO_2 and a decrease in pH, and the constrictor stimulus of a rise in O_2 tension. Despite the fact that the rise in pO_2 must have been several times as great as the increase in pCO_2, the resultant effect was dilator in most of the patients. Excluding the two patients (J. B. and I. H.) in whom the CVR rose with oxygen, the mean CVR values with air and oxygen breathing were 1.2 and 0.9 mm. Hg/cc./100 gm./minute, respectively.

Although the $CMRO_2$ during air breathing was below the control mean in seven of the nine patients, definite conclusions based on the small difference between the means are probably not warranted. Some reduction in $CMRO_2$ would not be surprising in chronically ill patients with long-standing abnormalities in the blood gas tensions. There was no evidence that over-all cerebral metabolism, as indicated by the $CMRO_2$, was adversely affected by the relatively brief (30-minute) period of oxygen inhalation. It is of interest that in the one patient (C. M.) whose mental status became worse with oxygen there was an associated rise in cerebral oxygen consumption.

The increases in cerebrospinal fluid pressure

with change in the inspired gas from air to oxygen also favor the conclusion that cerebral vasodilator effects were dominant during the period of oxygen breathing. The pressure changes, however, were in general moderate and in no case were extreme levels reached, such as have been reported by other workers.[3]

SUMMARY

1. The cerebral blood flow (CBF), oxygen consumption ($CMRO_2$) and vascular resistance (CVR) were determined by the nitrous oxide technic before and during the administration of 85 to 100 per cent oxygen in nine patients with chronic pulmonary emphysema and in eight control subjects.

2. In the patients with emphysema the mean CBF was significantly elevated, while the mean $CMRO_2$ was slightly below control values. There was a tendency for the emphysematous patients with the lowest arterial pO_2 and the highest pCO_2 values to show the highest blood flow values. The converse was also true.

3. Inhalation of 85 to 100 per cent oxygen was generally followed by an increase in CBF in the patients with emphysema in contrast to the control patients in whom the CBF decreased. Two emphysematous patients who had the lowest CBF values while breathing air showed a decrease in CBF during inhalation of oxygen.

4. The mean $CMRO_2$ did not change in either group of patients with oxygen administration. One patient with emphysema exhibited mental aberrations which may have been aggravated by oxygen therapy. Oxygen caused an increase in spinal fluid pressures in the patients with emphysema and either no change or a fall in spinal fluid pressures in the control subjects.

5. Oxygen inhalation caused a depression of pulmonary ventilation in the patients with emphysema and resulted in a rise in arterial pCO_2 and a fall in pH. The moderate increase in pCO_2 and decrease in pH apparently more than offset the large increase in pO_2 and thus brought about a rise in cerebral blood flow.

Acknowledgments: We wish to express appreciation to Drs. Joseph T. Doyle, Jr. and Joseph S. Wilson for supplying the data on pulmonary arterial pressure and cardiac output in two patients. We are indebted to Misses Mary McPhaul, Voncile Williams, Mary Fordham and to Mrs. Louise Thompson and Mrs. Fransetta Latimer for technical assistance, and to Miss Ann Payne for her work on the illustrations.

REFERENCES

1. Kety, S. S. and Schmidt, C. F. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. *J. Clin. Investigation*, 27: 484, 1948.
2. Baldwin, E. deF., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. III. A study of 122 cases of chronic pulmonary emphysema. *Medicine*, 28: 201, 1949.
3. Davies, C. E. and Mackinnon, J. Neurological effects of oxygen in chronic cor pulmonale. *Lancet*, 2: 883, 1949.
4. Comroe, J. H., Jr., Bahnson, E. R. and Coates, E. O., Jr. Mental changes occurring in chronically anoxemic patients during oxygen therapy. *J. A. M. A.*, 143: 1044, 1950.
5. Barach, A. L. The treatment of anoxia in clinical medicine. *Bull. New York Acad. Med.* 26: 370, 1950.
6. Richards, D. W., Jr. Inhalational therapy in cardiac diseases. Cardiac failure. *Bull. New York Acad. Med.*, 26: 384, 1950.
7. Kety, S. S. and Schmidt, C. F. The nitrous oxide method for the quantitative determinations of cerebral blood flow in man: theory, procedure and normal values. *J. Clin. Investigation*, 27: 476, 1948.
8. Patterson, J. L., Jr., Heyman, A. and Nichols, F. T., Jr. Cerebral blood flow and oxygen consumption in neurosyphilis. *J. Clin. Investigation*, 29: 1327, 1950.
9. Peters, J. P. and Van Slyke, D. D. Quantitative Clinical Chemistry, vol. II, Methods. Baltimore, 1932. Williams & Wilkins.
10. Orcutt, F. S. and Waters, R. M. A method for the determination of cyclopropane, ethylene, and nitrous oxide in the blood with the Van Slyke-Neill manometric apparatus. *J. Biol. Chem.*, 117: 509, 1937.
11. Singer, R. B. and Hastings, A. B. An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. *Medicine*, 27: 223, 1948.
12. Handbook of Respiratory Data in Aviation. National Research Council, 1944. Washington, D.C.
13. Singer, R. and Hastings, A. B. Material for Handbook of Biological Data, to be published. Quoted by Comroe, J. H., Jr. Pulmonary function tests. *Am. J. Med.*, 10: 356, 1951.
14. Kety, S. S., Polis, D. B., Nadler, C. S. and Schmidt, C. F. The blood flow and oxygen consumption of the human brain in diabetic acidosis and coma. *J. Clin. Investigation*, 27: 500, 1948.
15. Scheinberg, P. Cerebral circulation in heart failure. *Am. J. Med.*, 8: 148, 1950.

Pulmonary Function in Patients Convalescing from Acute Poliomyelitis with Respiratory Paralysis*

DANIEL S. LUKAS, M.D.† *and* FRED PLUM, M.D.

New York, New York

(with the technical assistance of Dolores Lukas)

AUTOPSY examination has demonstrated acute pulmonary emphysema, pulmonary edema and often atelectasis and pneumonitis in patients dying of acute poliomyelitis.[1–3] Usually such patients have been in mechanical respirators for several hours before death, and almost invariably they have suffered at least brief periods of asphyxia. Whether the abnormalities found in the lungs are caused by the mechanical respirators or by poliomyelitis *per se* has not been ascertained.

The present study was undertaken in order to delineate the patterns of pulmonary function associated with respiratory paralysis following acute poliomyelitis and to determine whether artificial respiration or other factors produced physiologically significant intrapulmonary changes in these patients.

MATERIAL AND METHODS

Pulmonary function studies were performed in twelve patients whose ages ranged from six to thirty-four years, all of whom suffered some degree of paralysis of the respiratory musculature as the result of acute poliomyelitis. Brief case histories of these patients will follow. Pulmonary function was determined in each case between the second and eleventh month of convalescence.

The patients were placed in three categories based on whether they had needed artificial respiration during the acute stage of their disease, the results of vital capacity and fluoroscopic examination of the chest prior to the pulmonary function studies. Group I includes patients who did not need artificial respiration during their acute illness but who suffered definite paralysis of part of the diaphragmatic or intercostal musculature. Group II includes patients who needed artificial respiration for only relatively brief periods of time during and after the acute illness (twenty days maximum in the tank respirators), and had moderately severe residual respiratory muscle paralysis at the time of study. Group III includes patients who required artificial respiration for long periods and who had severe residual limitation of breathing with a clinical estimation of ventilatory function of less than 50 per cent of normal at the time of the study. Two patients included in this group continued to need intermittent artificial respiration. (Table I.)

Each of the twelve patients had associated paralysis of other muscle groups, usually in proportion to the extent of the respiratory paralysis. Shortly prior to pulmonary function studies physical examination, fluoroscopy and roentgenograms of the chest revealed no evidence of parenchymal pulmonary disease.

Each subject was studied in the basal state. Lung volumes, maximum breathing capacity (MBC), index of intrapulmonary mixing (IIPM), and ventilation were determined by methods previously described.[4] All lung and ventilatory volumes were converted to BTPS (body temperature, ambient barometric pressure, saturated with water) and compared to available normal and predicted values.[4,5] Analysis of inspired and expired air was performed with the 0.5 cc. Scholander microgas analyzer.[6] Arterial

* From the Cardio-Pulmonary Laboratory of the Departments of Radiology and Medicine, and the Poliomyelitis Service of the New York Hospital-Cornell Medical Center, New York, N. Y. This study was aided by a grant from the New York Heart Association.

† Work completed during tenure of a Post-Doctorate Research Fellowship of the National Heart Institute.

blood was obtained from the brachial artery through an inlying needle and was submitted to analysis for carbon dioxide content, oxygen content and oxygen capacity.[7] Arterial blood pH was determined with the Cambridge research model pH meter. Carbon dioxide tension

TABLE I

CLINICAL DATA

Group	Patient, Age & Sex	Respiratory Paralysis*			Estimated Remaining Function (%)
		Diaphragm Left	Diaphragm Right	Intercostals	
I	F. R., 19, F	1+	0	1+	70
	M. O., 23, F	1+	1+	3+	75
	I. R., 30, F	1+	1+	1+	70
II	J. T., 14, F	0	1–2+	0	70
	M. T., 25, F	0	1+	3–4+	80
	I. P., 18, M	3+	1+	2+	60
	E. L., 32, F	4+	0–1+	1+	60
III	F. C., 6, M	3+	3+	3+	40
	G. R., 14, M	4+	1+	2+	40
	M. D., 33, M	3–4+	3–4+	2+	30
	O. S., 10, M	4+	4+	3–4+	20
	G. H., 23, M	4+	4+	3–4+	10

*1+ slight paralysis; 2+ moderate paralysis; 3+ severe paralysis; 4+ complete paralysis.

(pCO_2) and oxygen tension (pO_2) of arterial blood were determined by the micromethod of Riley.[8] This method has been modified in our laboratory by the use of a Vernier scale mounted on the side of the 37°c. water bath, enabling the analyst to read the length of the gas bubble in the capillary to the nearest 0.02 mm.

With the respiratory exchange ratio (R. Q.) of the expired air and the pCO_2 and pO_2 of simultaneously collected arterial blood, it was possible to calculate the mean alveolar pO_2, the alveolar-arterial oxygen gradient and venous admixture to total pulmonary blood flow.[9] Since mixed venous blood was not obtained, an oxyhemoglobin saturation value of 25 per cent lower than arterial saturation was assumed in the latter calculation.[10] A specially constructed small dead space respiratory valve was used in the collection of expired air in order to make possible physiologic dead space determination.

To determine the response to exercise, oxygen saturation and tension of arterial blood and ventilation were measured during a steady state of flexing and extending the legs or one leg and an arm in those patients capable of performing such movement.

RESULTS

Lung Volumes. The vital capacity was significantly reduced in all but one instance, the degree of reduction roughly paralleling the degree of respiratory muscle paralysis. (Table II., Fig. 1.) Severe or complete paralysis of one leaf of the diaphragm was associated with a 50 per cent reduction in vital capacity. With complete paralysis of both leaves of the diaphragm and marked intercostal muscle weakness, Cases O. S. and G. H. were able to effect vital capacities 21 and 11 per cent of predicted with their accessory respiratory musculature.

The residual volume was increased from 125 to 280 per cent in all but two of the patients. The magnitude of residual volume bore no relationship to the extent of respiratory paralysis nor to the previous use of a respirator. Total lung capacity (TC) was essentially normal in the patients in Group I and decreased in the patients in Groups II and III. Total capacity suffered a smaller decrease than did vital capacity because of the large residual volume.

The ratio of residual volume to total lung capacity (RV/TC) was large in all subjects and in nine it exceeded 35 per cent. An RV/TC ratio greater than 35 per cent is commonly regarded as indicating overdistention or emphysema of the lungs.[11] There are several reasons for not applying this criterion to the present group of patients. In the first place their increased residual volumes were due to inability to expire completely, the result of paralysis of muscles (abdominals) which normally aid in complete expulsion of air from the chest bellows. This is substantiated by the average reduction of 540 cc. in the expiratory reserve volume (reserve air). The effect of loss of expiratory ability on residual volume is illustrated in Figure 1 in which it can be seen that the decrease in expiratory reserve volume was almost equal to the increase in residual volume. The functional residual capacity (i.e., residual volume plus expiratory reserve volume) was consequently not increased except in Cases I. R. and J. T. who were regarded as having residual volumes much greater than could be explained on the basis of paralysis of expiratory muscles. Finally, when the total lung capacity is de-

creased by some abnormal process, the residual volume, if it is not proportionately decreased, will comprise a larger than normal fraction of total capacity. True emphysema associated with pulmonary parenchymal changes was therefore probably not present, but the interrelationship among the subdivisions of total lung capacity were of a *physiologically* emphysematous pattern.

Ventilatory Function. MBC was below normal in all subjects but was relatively better preserved than vital capacity in all save three patients. (Table III.) Despite the loss of one-half of their diaphragmatic function some individuals were able to achieve an MBC of more than 75 per cent of normal; the two subjects with complete diaphragmatic paralysis achieved 32 and 25 per cent of normal with the use of their accessory respiratory muscles. In absolute terms, however, the MBC in these subjects was extremely small.

Poor correlation between MBC and vital capacity has been observed repeatedly in various pulmonary diseases.[12–14] The low order of correlation between the values of the two tests, in absolute terms ($r = 0.641 \pm 0.178$; $p = .03$) or in per cent of predicted ($r = 0.478 \pm 0.246$; $p = > .05$), demonstrated in the present study further indicates that the spatial limits of the lungs is only one of the several factors influencing

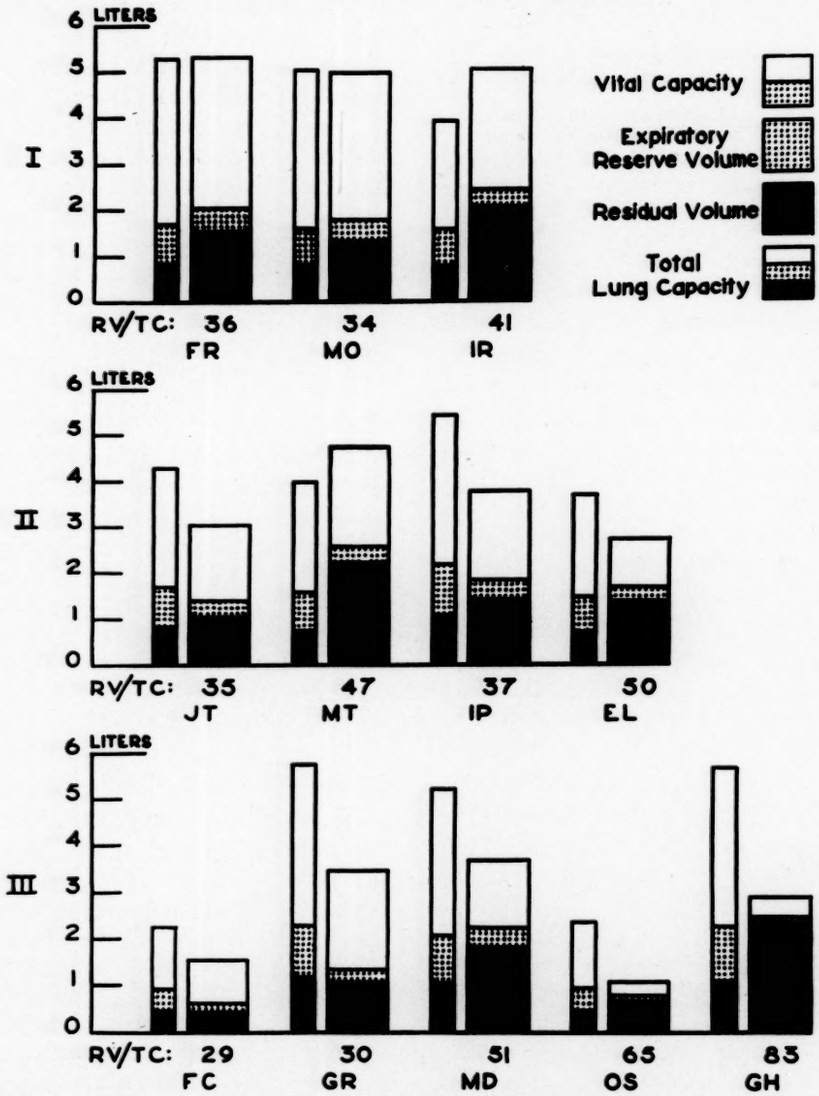


FIG. 1. Lung volumes: the narrow vertical columns represent predicted normal values; the wide columns, observed values. Normal RV/TC ratios (20.0 to 20.4 per cent) are not shown.

ventilatory function. Dyspnea is directly related to a reduced MBC. Those subjects whose residual non-respiratory paralysis did not greatly restrict their activity and who had a poor MBC complained of exertional dyspnea. The physical activity of many of the patients was so confined, however, as not to place a significant burden on their ventilatory apparatus.

TABLE II

OBSERVED AND PREDICTED LUNG VOLUMES

Group	Patient	Vital Capacity			Residual Volume			Total Capacity			RV/TC (%)	
		Observed	Predicted	Observed/ Predicted (%)	Observed	Predicted	Observed/ Predicted (%)	Observed	Predicted	Observed/ Predicted (%)	Observed	Predicted
I	F. R.	2777	3406	81	1531	852	180	4308	4258	101	35.5	20.0
	M. O.	2650	3212	82	1338	803	167	3988	4015	99	33.6	20.0
	I. R.	2983	3096	96	2037	774	263	5020	3870	130	40.6	20.0
II	J. T.	1990	3440	58	1077	860	125	3067	4300	71	35.1	20.0
	M. T.	2516	3204	78	2241	801	280	4757	4005	119	47.1	20.0
	I. P.	2372	4360	54	1398	1090	128	3770	5450	69	37.1	20.0
	E. L.	1357	2968	46	1386	742	187	2752	3710	74	50.4	20.0
III	F. C.	1075	1800	60	443	461	96	1518	2261	57	29.2	20.4
	G. R.	2430	4600	53	1052	1150	91	3482	5750	61	30.2	20.0
	M. D.	1824	4196	44	1858	1049	177	3682	5245	69	50.5	20.0
	O. S.	391	1890	21	710	480	148	1101	2371	46	64.5	20.4
	G. H.	493	4517	11	2400	1130	212	2893	5647	51	83.0	20.0
Average		1905	3391	57	1456	849	171	3362	4240	79	44.7	20.0

Alveolorespiratory Function. Of crucial importance in determining the presence of physiologically significant intrapulmonary disease is a definition of the pattern of alveolorespiratory function, namely, the distribution of air among the alveoli and exchange of the respiratory gases across the alveolar membrane.

Mixing of gases within the lungs of all subjects was normal as indicated by the low indices of intrapulmonary mixing. (Table III.) Indeed, these values are very low, and since the expiratory ability of the subjects was impaired they may not represent true alveolar air samples. It is possible that more sensitive methods of assessing intrapulmonary mixing, such as those using the continuous recording nitrogen analyzer, would have revealed some defects.[15]

Judging from the arterial oxyhemoglobin saturation, oxygenation of the blood was below the lower limit of normal (92 per cent) in only two patients, each of whom had severe or moderately severe paralysis. However, the directly determined oxygen tension of the arterial blood, which is a more sensitive index of oxygenation, revealed varying degrees of anoxemia in five of the patients in Groups II and III. The anoxemia was associated with low alveolar oxygen tensions, slight to moderate elevation of alveolar and arterial carbon dioxide tensions and respiratory acidosis. (Tables IV and V.) In Case F. C. the small elevation of alveolar-arterial oxygen gradient indicated the existence of slightly defective oxygen diffusion or the persistence of blood flow through underventilated areas of the lungs. Some reservation must be made in the interpretation of the data in this patient since reported findings of similar studies on normal children of this extremely young age group are not available. In the remaining four subjects with anoxemia normal values for alveolar-arterial oxygen gradient argue against the presence of impeded oxygen diffusion or incomplete oxygenation of capillary blood in underventilated alveoli. These mechanisms, therefore, could not be responsible for their anoxemia. It is indicated by the large dead space/tidal volume ratios in the presence of normal values for *physiologic* dead space that the tidal volumes of these subjects were too small for maintaining normal gas exchange. (Table

v.) A state of overall and fairly uniform underventilation of the alveoli, therefore, accounted for their anoxemia and hypercapnia.

able to increase his arterial oxygen tension to normal. This was accomplished through a twofold increment in alveolar ventilation effected

TABLE III

MAXIMUM BREATHING CAPACITY, BASAL VENTILATION AND IIPM

Group	Patient	MBC in L/Min.			Ventilation in L/Min./M^2		IIPM*
		Observed	Predicted	Observed/Predicted (%)	Observed	Predicted	
I	F. R.	56	97	58	5.7	3.2	0.7
	M.O.	86	98	88	4.5	3.2	0.8
	I. R.	36	93	39	---	---	0.9
II	J. T.	71	95	75	---	---	1.0
	M. T.	70	98	71	4.4	3.2	1.3
	I. P.	98	124	79	3.1	3.6	0.8
	E. L.	62	81	77	3.8	3.2	1.3
III	F. C.	36	50	73	5.7	4.9	1.1
	G. R.	73	124	59	4.1	4.0	0.8
	M. D.	55	111	49	---	---	1.5
	O. S.	18	58	32	4.9	4.9	1.2
	G. H.	28	113	25	4.0	3.6	1.2
Average		57	95	60	4.5	3.8	1.1

*Normal IIPM: < 2.5%

It is of interest that during an exercise that increased oxygen consumption by only 67 cc. /min./sq.m. body surface area, Case I. P. was

TABLE IV

ARTERIAL OXYHEMOGLOBIN SATURATION, pH AND pCO_2*

Group	Patient	O_2 Sat. (%)		pH		pCO_2 (mm. Hg)	
		Rest	Exercise	Rest	Exercise	Rest	Exercise
I	F. R.	98	97	7.53	7.62	33	26
	M. O.	92	98	7.43	7.52	36	--
II	M. T.	99	98	7.40	7.46	38	32
	I. P.	91	95	7.33	7.37	47	45
	E. L.	96	99	7.36	7.35	42	44
III	F. C.	95	--	7.37	---	41	--
	G. R.	95	92	7.39	7.36	43	46
	O. S.	87	--	7.35	---	58	--
	G. H.	93	--	7.32	---	43	--
Average		94	96	7.39	7.44	43	39

*Resting normal values: O_2 Sat.: 96%
pH : 7.42
pCO_2 : 40 mm. Hg

by doubling the respiratory rate without change in tidal volume. Thus it appears that this subject was adjusted to a state of chronic hypoventilation at rest.

In contrast one of the patients in Group I showed low alveolar and arterial carbon dioxide tensions, elevated oxygen tensions and considerable hyperventilation, probably the result of anxiety. (Tables III to V.) She had a large dead space/tidal volume ratio that was associated with a large *physiologic* dead space. In this subject alveolar ventilation was more than adequate and overventilated alveoli acted as dead space by virtue of an air supply greater than that required by the quantity of blood flowing through them.

COMMENTS

From the data it would appear that characteristic alterations in lung volumes and pulmonary function develop in patients recovering from acute anterior poliomyelitis associated with respiratory paralysis. These alterations include reduction in vital capacity in proportion to the residual paralysis of the respiratory muscles, significantly increased residual vol-

umes and diminished ventilatory function. In the moderately to severely paralyzed patients chronic alveolar hypoventilation associated with small tidal volumes, mild to moderate arterial anoxemia, elevated carbon dioxide tension and respiratory acidosis is frequently present.

limitations on thoracic movements and rate of gas exchange similar to emphysema.

Two patients had residual volumes too large to be explained by a reduction in expiratory reserve volume. Functional residual capacities were increased in both. In one the finding remains unexplained. The other, who had never been in a respirator, had suffered from repeated respiratory infection following discharge from the hospital and complained of considerable exertional dyspnea. On clinical grounds it was suspected that chronic bronchial infection with secondary emphysema had developed. The low MBC, essentially normal vital capacity and large RV/TC ratio corroborate this clinical opinion.

TABLE V

ALVEOLAR AND ARTERIAL OXYGEN TENSIONS AND ALVEOLAR VENTILATION-PERFUSION RELATIONSHIPS*

Group	Patient	Alveolar pO_2 (mm. Hg)	Arterial pO_2 (mm. Hg)	Alveolar-Arterial O_2 Gradient (mm. Hg)	Dead Space (cc.)	Dead Space / Tidal Volume (%)	Venous Admixture / Pulmonary Blood Flow (%)
I	F. R.	116 (125)†	106 (113)	10 (12)	197	35	2.7
	M. O.	107	93	14	183	25	4.2
II	M. T.	106 (119)	92 (99)	14 (20)	---	—	4.6
	I. P.	78 (95)	73 (90)	5 (5)	113	30	5.7
	E. L.	96 (95)	87 (89)	9 (6)	150	35	2.7
III	F. C.	99	82	17	45	20	7.4
	G. R.	101 (92)	94 (88)	7 (4)	99	25	2.7
	O. S.	75	66	9	56	35	9.1
	G. H.	86	83	3	117	37	3.8
Average		96 (105)	86 (96)	10 (9)	120	30	4.8

*Normal resting values: Alveolar pO_2 – 104 mm. Hg
Arterial pO_2 – 95 mm. Hg
Alveolar–arterial O_2 Gradient – 9 mm. Hg
Dead space/Tidal volume – <30%
Venous admixture/Pulmonary blood flow – <7%

†Values in parentheses observed during exercise.

At first it was suspected that the large residual volumes and RV/TC ratios represented emphysematous changes similar to those observed on postmortem examination of the lungs of patients who have been in respirators.[2,3] The finding of similarly expanded residual volumes in individuals who did not receive artificial respiration argues against this view. It appears that the diminished expiratory reserve volume incident to paralysis of the accessory muscles used in forced expiration explains the increase in residual volumes. Since the patient could not expire completely, more air remained in his lungs. On the basis of these considerations and the absence of significantly increased alveolar-arterial oxygen gradients invariably noted in pulmonary fibrosis, there is no evidence that poliomyelitis *per se* or the use of artificial respirators operating on a cyclic negative pressure principle produce any parenchymal disease. The changes in vital capacity and residual volume relative to total capacity are of a type physiologically associated with emphysema and impose

Because of weak cough and limited respiratory excursions patients recovering from poliomyelitis with respiratory paralysis are susceptible to recurrent respiratory infections. The bronchiolar narrowing and obstruction that such infections may cause lead to anoxemia and carbon dioxide retention which the normal individual overcomes by alveolar hyperventilation. In the patient whose level of gas exchange is either barely normal or subnormal because of a crippled ventilatory apparatus, such infections may lead to respiratory insufficiency severe enough to constitute a serious threat to life. The need for oxygen therapy and adequate

artificial ventilation under such circumstances is well borne out by clinical experience. Bouts of tracheobronchitis and bronchopneumonia occurring in the late convalescent phase of some of the patients reported precipitated such marked respiratory embarrassment that it was necessary to return them to the respirator and to administer oxygen. In one instance a healed tracheotomy was reopened to provide for adequate drainage of bronchial secretions and purulent matter.

Another danger incident to respiratory infections in individuals with respiratory paralysis is the development of structural lung changes which will lead to marked accentuation of pulmonary disability. Therefore, at the first sign of a respiratory infection patients who have suffered any paralysis of breathing should receive immediate measures, such as postural drainage and bronchodilators, aimed at maintaining patency of the pulmonary airways, and should be given antibiotics immediately.

There is a striking similarity between the pattern of pulmonary function following poliomyelitis with residual respiratory paralysis and that observed in advanced kyphoscoliosis of the thoracic cage, a common sequel to poliomyelitis in childhood.[16] The kyphoscoliotic is also susceptible to respiratory infections that are frequently fatal and is subject to the secondary development of structural pulmonary changes. When such changes develop, the marked pulmonary insufficiency and, eventually, the cardiac insufficiency that are associated with classic kyphoscoliotic heart disease ensue.

Since mild but functionally significant impairment of the respiratory muscles may not be immediately apparent clinically (Case I. R.), it is necessary to evaluate the extent of respiratory paralysis and the concomitant changes in pulmonary function in every patient recovering from poliomyelitis. It will be noted from a comparison of Table 1 and the data on function that fluoroscopy yielded considerable information about the state of the chest bellows of each patient. Careful fluoroscopy of the chest, estimation of the vital capacity and, if at all possible, MBC are recommended if more complete pulmonary function tests are not available. The information obtained from these procedures is of aid not only in measuring subsequent improvement or deterioration of pulmonary function in the individual patient but is also helpful in explaining symptomatology and in directing treatment.

CASE REPORTS

Group I

F. R., a nineteen year old female, seven months pregnant, was admitted on August 24, 1949. Moderate paralysis developed in all four extremities, the abdomen and back. Vital capacity fell to 1000 cc. during her acute illness but artificial respiration was not needed. A normal full term low forceps delivery took place on October 25, 1949. At the time of pulmonary function studies in May, 1950, the left diaphragm showed a peripheral lag on inspiration and lower intercostal activity was moderately reduced.

M. O., a twenty-three year old female, was admitted on October 7, 1949. Fairly marked paralysis developed in all four extremities, the abdomen and back. Her vital capacity fell to 1018 cc. on October 15, 1949, but thereafter rose and artificial respiration was not needed. At the time of pulmonary function studies in January, 1951, fluoroscopy revealed both diaphragms slightly limited in motion but intercostal muscle activity was markedly impaired.

I. R., a twenty-nine year old female, eight months pregnant, was admitted on August 8, 1949. Paralysis of moderate degree developed in both legs, the abdomen and back. A normal full term low forceps delivery took place on September 26, 1949. Recovery of muscle function in the lower extremities was rapid. It was not until after the patient had been discharged from the hospital and complained of dyspnea and difficulty in coughing with a respiratory infection that she was fluoroscoped. Fluoroscopy in April, 1950, revealed a moderate reduction in diaphragm motility on the right and a moderately severe loss of intercostal muscle activity. Although a chest x-ray was normal, this patient had had repeated attacks of tracheobronchitis since her poliomyelitis.

Group II

J. T., a fifteen year old female, was admitted on August 30, 1949. A progressive fall in vital capacity to 300 cc. developed within the next twenty-four hours. The patient received artificial respiration by tank respirator continuously for seventy-two hours and in progressively smaller daily amounts for the next nine days. She was intermittently on a rapid rocking Respiraid bed for ten additional days. Improvement was steady, but at the time of pulmonary function studies in February, 1950, she still had moderate

weakness of the legs and paralysis of the muscles of the abdomen. Fluoroscopy showed a moderate lag in the action of the left diaphragm and moderate lower intercostal weakness.

M. T., a twenty-five year old woman, was admitted on November 15, 1949. During the next four days, progressive difficulty in breathing developed. On November 20th the patient was transferred from a rocking bed to a tank respirator because of the development of respiratory acidosis. She was in a tank respirator continuously for forty-eight hours, intermittently for eight days more and then on a rocking bed intermittently for a total of fourteen days in convalescence. She had moderately severe weakness of both arms, abdominal muscles and the right leg. Fluoroscopy, just prior to function studies in March, 1950, revealed a moderate reduction of the activity of the right diaphragm and poor intercostal function.

I. P., an eighteen year old male, was admitted on September 10, 1949. He was placed in a tank respirator on September 12th for four days continuously, and intermittently for fifteen more. He was intermittently on a rocking bed for fourteen days. At the time of pulmonary function studies in February, 1950, fluoroscopy of the chest revealed slight limitation of movement of the left diaphragm and moderate limitation of the right; intercostal function was only slightly impaired.

E. L., a thirty-two year old woman, was admitted on August 30, 1950. The day following admission her vital capacity fell to 518 cc. and for the next two days she required a tank respirator for twelve hours daily. For five additional days a rocking bed was necessary to assist her ventilation. At the time of pulmonary function tests in October, 1950, the patient had marked weakness of the left arm and moderate abdominal weakness. Fluoroscopy revealed paradoxical movement of the left diaphragm, slight reduction of movement of the right diaphragm and reduced upper intercostal muscle activity.

Group III

F. C., a six year old male, was admitted on September 4, 1949, having been placed in a tank respirator one month previously at another hospital. He continued to need artificial respiration delivered by a tank respirator or a rocking bed intermittently until November 5, 1949. In February, 1950, an acute bronchopneumonia developed which rapidly cleared on antibiotics. At the time of pulmonary function studies in May, 1950, the patient had severe residual paralysis of both legs, the abdomen and the right arm. Fluoroscopy revealed a marked bilateral reduction in diaphragm activity and moderate limitation of motion of the lower intercostals.

G. R., a fourteen year old male, was admitted October 10, 1949, with severe residual paralysis of both legs and trunk, and moderate paralysis of the arms. He had been in a tank respirator for sixteen days at another hospital during his acute illness one month previously and needed the rocking bed for assistance in ventilation intermittently for twenty-five days at this institution. At the time of pulmonary function tests in March, 1950, he had moderate residual paralysis in the lower extremities and abdomen. Fluoroscopy revealed bilateral reduction of diaphragm activity, with only minimal movement of the right and moderate reduction of intercostal activity.

M. D., a thirty-three year old male, was admitted on August 3, 1949. A respiratory insufficiency rapidly developed and the patient was placed in a cuirass respirator in which he remained for thirty days. He was then transferred to a tank respirator which was required intermittently for an additional fifty-two days. The patient was started in a rocking bed shortly after his transfer to a tank respirator and needed that device for periodic respiratory assistance for sixty-eight days. A tracheotomy had been performed at the time of onset of the respiratory insufficiency. The patient contracted bronchopneumonia at the time of his acute illness; and during another bout of bronchopneumonia in December, 1949, the tracheotomy had to be reopened to establish drainage. At the time of pulmonary function studies in March, 1950, he still suffered severe residual paralysis of the extremities and trunk. Fluoroscopy showed only minimal bilateral diaphragmatic activity and severe lower intercostal paralysis.

O. S., a ten year old boy, was admitted on August 2, 1949, and almost immediately needed artificial respiration supplied by a cuirass respirator for two days and tank respirator continuously for twenty-nine days. His ventilation slowly improved but at the time of pulmonary function studies in March, 1950, he still needed a tank respirator at night and intermittent periods in the rocking bed daily. Tracheobronchitis developed in March, 1950, which re-

sponded to antibiotic therapy. At the time of function studies fluoroscopy revealed essentially no diaphragmatic or lower intercostal activity, breathing being accomplished almost entirely by the accessory muscles of respiration.

G. H., a twenty-four year old male, was admitted on September 9, 1949, and at the time had been constantly in a tank respirator for forty-one days. He continued to need artificial respiration for an additional thirty-three days and required daily intermittent periods in the rocking bed and in the respirator until the time of pulmonary function studies in March, 1950. At that time he had a severe quadriplegia and paralysis of the trunk. Fluoroscopy showed no apparent motion of the diaphragm and lower intercostal muscles, breathing being effected almost entirely by the accessory muscles of respiration.

SUMMARY

1. Pulmonary function studies were performed in twelve patients convalescing from acute poliomyelitis with varying degrees of respiratory paralysis.

2. Lung volume analysis revealed reduction of vital capacity in all but one instance. Residual volume was increased from 125 to 280 per cent in all but two subjects. The expiratory reserve volume was decreased by an average of 540 cc. The increased residual volumes were associated with paralysis of muscles effecting forced expiration and did not represent structural emphysema.

3. Maximum breathing capacity was below normal but in general was relatively better preserved than vital capacity, with which it correlated poorly.

4. The pattern of mixing and diffusion of gases in the lungs was normal, but alveolar ventilation was inadequate in five of the moderately and severely paralyzed patients, as indicated by low oxygen and elevated carbon dioxide tensions in the alveoli and the arterial blood.

5. There was no evidence that poliomyelitis *per se* or mechanical respirators acting on a cyclic negative pressure principle produced any physiologically significant intrapulmonary defects.

6. The state of the respiratory musculature of every patient recovering from poliomyelitis should be determined because slight but important degrees of paralysis may not be recognized. Fluoroscopy of the chest and vital capacity are simple and reliable methods for this evaluation.

REFERENCES

1. Harper, P. and Tennant, R. Treatment of respiratory failure in poliomyelitis. *Yale J. Biol. & Med.*, 6: 31, 1933.
2. Brown, J. R. and Baker, A. B. Poliomyelitis. I. Bulbar poliomyelitis. *J. Nerv. & Ment. Dis.*, 109: 54, 1949.
3. Plum, F. and Lukas, D. S. An evaluation of the cuirass respirator in acute poliomyelitis with respiratory insufficiency. *Am. J. M. Sci.*, 221: 417, 1951.
4. Baldwin, E. de F., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. I. Physiological classification, clinical methods of analysis, standard values in normal subjects. *Medicine*, 27: 243, 1948.
5. Lester, C. W., Cournand, A. and Riley, R. L. Pulmonary function after pneumonectomy in children. *J. Thoracic Surg.*, 11: 529, 1942.
6. Scholander, P. F. Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter sample. *J. Biol. Chem.*, 167: 235, 1947.
7. Peters, J. P. and Van Slyke, D. D. Quantitative Clinical Chemistry, vol. II, Methods. Baltimore, 1932, Williams & Wilkins Co.
8. Riley, R. L., Proemmel, D. D. and Franke, R. E. A direct method for determination of oxygen and carbon dioxide tensions in blood. *J. Biol. Chem.*, 161: 621, 1945.
9. Riley, R. L., Cournand, A. "Ideal" alveolar air and the analysis of ventilation-perfusion relationships in the lungs. *J. Appl. Physiol.*, 1: 825, 1949.
10. Cournand, A., Riley, R. L., Himmelstein, A. and Austrian, R. Pulmonary circulation and alveolar ventilation-perfusion relationships after pneumonectomy. *J. Thoracic Surg.*, 19: 80, 1950.
11. Baldwin, E. de F., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. III. A study of 122 cases of chronic pulmonary emphysema. *Medicine*, 28: 201, 1949.
12. Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. II. The effects of various types of collapse therapy upon cardiopulmonary function. *Am. Rev. Tuberc.*, 44: 123, 1941.
13. Matheson, H. W., Spies, S. M., Gray, J. S. and Barnum, D. R. Ventilatory function tests. II. Factors affecting the voluntary ventilation capacity. *J. Clin. Investigation*, 29: 682, 1950.
14. Gaensler, E. A. Air velocity index. *Am. Rev. Tuberc.*, 62: 17, 1950.
15. Fowler, W. S. Lung function studies. III. Uneven pulmonary ventilation in normal subjects and in patients with pulmonary disease. *J. Appl. Physiol.*, 2: 283, 1949.
16. Chapman, E. M., Dill, D. B. and Graybiel, A. The decrease in functional capacity of the lungs and heart resulting from deformities of the chest: Pulmonocardiac failure. *Medicine*, 18: 167, 1939.

Venous Thrombosis in the Upper Extremities as a Complication of Myocardial Failure*

WILLIAM E. LORING, M.D.†
Syracuse, New York

VENOUS thrombosis occurring in the lower extremities is a relatively common finding. Thrombosis of the veins of the upper extremities is seen much less frequently. Matas[1] citing Lubarsch states that 90 per cent of thromboses occur in the lower extremities and elsewhere, and only 10 per cent occur in the upper extremities. Bouchut[2] places the ratio between the two areas at 50:1. Barker and his associates,[3] after a statistical analysis of 1,260 cases, found that the lower extremities were the site of 85.6 per cent of the thromboses and the upper extremities were the site of 1.7 per cent. The estimates of the latter two are probably more accurate. Of those occurring in the upper extremities by far the largest number is caused by an associated malignant tumor or trauma.[4] Thrombosis arising in this region, as a direct complication of myocardial insufficiency, is commensurably rare but probably not as rare as the number of reported cases would indicate.

A review of the literature has yielded eighty-three cases to which four cases observed and autopsied at the New York State University Medical Center at Syracuse have been added. As this complication of heart failure poses not only an interesting but a serious problem and as the subject has been a somewhat neglected one, it is believed that an analysis of the material now available will aid in clarifying the condition as a primary step toward understanding its cause and prevention.

LITERATURE

Bouchut[2] in 1845 reported the first case appearing in the literature. It was an example of massive thrombosis of the veins of both arms, both sides of the neck and the superior vena cava in a male. The patient was in severe cardiac decompensation but at the time of this report Bouchut failed to appreciate the importance of their simultaneous occurrence. Subsequent cases were reported;[5–15] cases reported by Peter, Robert, Parmentier, Mader and Kahn were summarized by Welch,[16] and cases reported by Hanot, Audral, Dreyfus, Potherat, Gallavardin and Peters were summarized by Sladen and Winternitz[17] in their respective reviews of the literature.

The first comprehensive consideration of the subject was undertaken by Welch[16] in 1900. He reviewed twenty cases that had been previously reported and added four more that had come to his personal attention. While discussing Welch's paper, Kinnicut[16] and Biggs[16] each described an additional case. Within the following ten-year period further contributions were made.[18–26]

Sladen and Winternitz[17] in 1916 again reviewed the literature and added to it thirteen cases, eleven of which were observed at the Johns Hopkins Hospital. In several of Welch's and Sladen and Winternitz's cases the thromboses did not occur in the upper extremities. These are not included in this series.

Perry and his associates[27] in 1933 reported a case occurring in a young girl with subacute bacterial endocarditis. Finlay[28] and Towers and Oldfield[29] in 1937 described two cases of subclavian vein thrombosis complicating cardiac failure secondary to hyperthyroidism. Veal[30] in 1940 reported seventeen cases of thrombosis of the axillary and subclavian veins from several causes. Five of these were attributed to heart disease. Veal and Hussey[4] in 1943 collected twenty-nine additional cases, eleven of which complicated congestive heart failure. With the addition of the five cases previously reported by

* From the Department of Pathology, State University of New York, Medical Center at Syracuse University, Syracuse, N. Y.
† Present address: Department of Pathology, Yale University School of Medicine, New Haven, Conn.

Veal, their series of cases caused by heart disease totaled sixteen. The thrombosis in two of these patients followed intravenous administration of mercupurin. In one patient a local infection was believed to be the inciting cause. DeBakey et al.[31] in the same year reviewed the subject

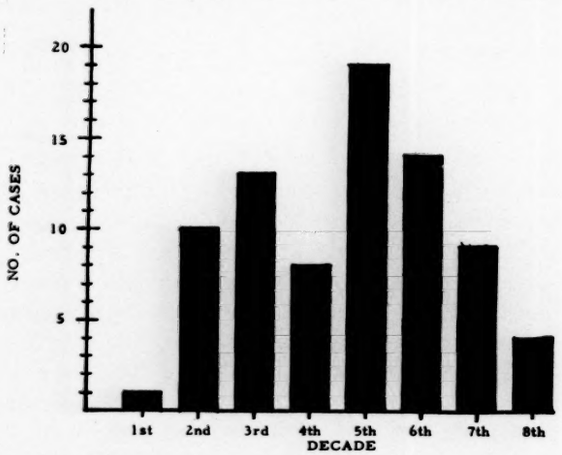


FIG. 1. Graph showing age distribution in seventy-eight cases.

of primary thrombosis of the axillary vein and included a case with spontaneous onset occurring in a sixty-six year old white female with hypertensive cardiovascular disease and auricular fibrillation. Esselborn and Janchar[32] in 1946 published a detailed report of the case of a forty-two year old colored female with coronary arteriosclerosis and an old myocardial infarction in whom the thrombotic process not only occluded the veins of the right arm and neck but also extended into the cranial cavity to involve the sigmoid and transverse sinuses and the veins of Galen.

Although the literature of the past thirty-five years abounds with case reports and reviews of so-called "effort thrombosis," interest in the subject of venous thrombosis of the upper extremity as a complication of heart disease has been limited.

Forty-nine of the eighty-seven collected cases came to autopsy. In nine cases the diagnosis was clinically confirmed by venography.

AGE, SEX AND RACE

In the seventy-eight cases in which the age was given the youngest was nine years and the oldest seventy-three years. The average age was 41.4 years. More than one-third of the cases occurred between forty and fifty-nine years. The distribution by decade is given in Figure 1.

There were two periods of peak incidence. The lesser occurred in the third, the greater in the fifth decade. The high incidence of cases in the third decade resulted from the frequent association of venous thrombosis with early rheumatic heart disease. The even greater incidence in the fifth decade could be attributed to the thromboses complicating not only late rheumatic heart disease but also the early degenerative myocardiopathies.

TABLE I

TYPES OF HEART DISEASE AND RELATIVE FREQUENCY OF EACH IN EIGHTY-THREE CASES

Types of Heart Disease	No. of Cases	Per cent
Rheumatic heart disease	45	54.2
Hypertensive cardiovascular disease	13	15.7
Chronic fibrous myocarditis	4	4.8
Mitral insufficiency	4	4.8
Syphilitic heart disease	3	
Coronary artery sclerosis	3	
Arteriosclerotic heart disease	2	
Thyrotoxic heart disease	2	
Myocardial degeneration	2	
Malignant hypertension	1	
Cor pulmonale	1	
Cardiac failure secondary to acute nephritis	1	
Aortic insufficiency and stenosis	1	
Aortic insufficiency	1	

The sex of the patient was given in eighty-five cases. Sixty-one (71.8 per cent) were females and twenty-four (28.2 per cent) were males. In view of the large number of patients in this series with rheumatic heart disease, this could partly be explained by the more frequent occurrence of mitral disease in women.

Forty-two patients were white, and sixteen were colored. The race was not given in twenty-nine.

TYPE OF CARDIAC LESION

The type of cardiac lesion was given in eighty-three cases. (Table I.) More than one-half of these (forty-five cases) were rheumatic heart disease. Hypertensive cardiovascular disease was the next largest group with thirteen cases. The remainder included syphilitic heart disease, coronary artery sclerosis, thyrotoxic heart disease, malignant hypertension, cor

pulmonale, cardiac failure secondary to acute nephritis, arteriosclerotic heart disease, chronic fibrous myocarditis and myocardial degeneration. In six cases only the valvular lesion was given. Some authors (notably Christian), perhaps not with complete justification, consider chronic fibrous myocarditis and hypertensive cardiovascular disease to be the same disease entity.

The cardiac disorder was given in some detail in sixty-six cases and was not available in twenty-one cases. As venous thrombosis rarely complicates hyperthyroidism, the two patients with thyrotoxic heart disease are of particular interest.

In the forty-five cases of rheumatic heart disease, the valvular lesions were given in forty cases as follows:

	No. of Cases
Mitral valve	40
Aortic valve	9
Tricuspid valve	11
Mitral Valve:	
Mitral insufficiency alone	12
Mitral stenosis alone	6
Both were present	22
Aortic Valve:	
Aortic insufficiency alone	7
Aortic stenosis alone	0
Both were present	2
Tricuspid Valve:	
Tricuspid insufficiency alone	7
Tricuspid stenosis alone	1
Both were present	3
Mitral valve alone	23
Mitral valve and aortic valve	6
Mitral valve and tricuspid valve	8
All three valves	3

In two cases the diagnosis was rheumatic myocarditis. In three cases the pathologic disturbance was not given.

The relative incidence of organic mitral valvular disease was high. This is of interest in view of the deleterious effect of this condition on pulmonary as well as circulatory efficiency.

Valvular lesions were also present in twelve non-rheumatic cardiac patients. In eleven of these patients the lesions were on a functional rather than an organic basis. The mitral valve was involved in seven, the aortic valve in four and the tricuspid valve in three cases. Mitral insufficiency occurred alone in five cases, aortic insufficiency alone in two and tricuspid insufficiency alone in two cases. Mitral insufficiency was combined with aortic insufficiency in one case and with tricuspid insufficiency in one case. Aortic insufficiency and stenosis were present in one case. Because the majority of these valvular lesions were on a functional rather than an organic basis, the part they played in the interference with circulation was secondary to myocardial deficiency. The types of heart disease found in this group were arteriosclerotic heart disease, cor pulmonale and cardiac failure complicating acute nephritis. The remainder are listed by valvular lesion in Table I.

TABLE II

FREQUENCY OF MORE SEVERE CARDIAC SYMPTOMS AS GIVEN IN FORTY-TWO CASES

Symptom	No. of Cases
Marked dyspnea	38
Dependent edema	37
Liver enlargement	28
Hydrothorax	25
Ascites	24
Orthopnea	11
Paroxysmal nocturnal dyspnea	6

In the fourteen cases in which no valvular lesion occurred the pathologic findings were given in some detail in seven. The common factors found in these were: (1) increase in cardiac weight with hypertrophy and dilatation of one or both ventricles, (2) fibrosis of the myocardium and (3) varying degrees of coronary artery sclerosis. The remaining seven cases were examples of rheumatic myocarditis, thyrotoxic heart disease and myocardial degeneration. Like the preceding group, the significant common denominator appeared to be functional myocardial insufficiency.

DEGREE AND DURATION OF HEART FAILURE

According to the standards set forth by the New York Heart Association,[33] eighty-five of the eighty-seven patients included in this series fall into class IV and could be considered in severe congestive failure. In forty-two of these sufficient clinical data were available to determine the frequency of seven of the more severe cardiac signs and symptoms. (Table II.)

As it is to be expected, cardiac enlargement was present in every patient. The frequency of the more severe signs and symptoms by patient was as follows: two patients had all seven, two had six, fourteen had five, eleven had four, six had three, five had two and two had one.

The relative frequency of hydrothorax is of some interest in view of its possible interference with venous return from the upper extremities and neck. This mechanism was first suggested by Welch.[16]

The duration of congestive failure was not given in thirty-six cases. In the remaining fifty-one cases it was sometimes vague, such as a "few weeks" or "several months." No exact determination of the period of broken compensation was therefore possible. A general idea can be obtained from the following breakdown of cases: five were given in terms of days, six in terms of weeks, twenty-three in terms of months and seventeen in terms of years. The shortest definite time period given was six days, the longest eight years.

TABLE III

DISTRIBUTION OF THROMBI AS THEY OCCURRED IN EIGHTY-SIX CASES

Vein	Left	Right	Bilateral	Total
Subclavian	45	20	5	70
Jugulars (internal and/or external)	25	17	9	51
Axillary	18	7	4	29
Innominate	9	6	7	22
Brachial	7	4	1	12
Basilic	0	2	0	2
Inferior thyroid	1	0	0	1
Superior vena cava	...	...	...	9

In approximately four-fifths of the cases in which the time element was given the myocordial failure had existed from several months to several years. In more than one-third of the patients it could definitely be considered a chronic condition. These findings indicate, therefore, that venous thrombosis of the upper extremity is much more likely to occur in patients with heart disease of long-standing.

LOCATION OF THROMBI

The left side alone was involved in fifty-one cases (58.6 per cent), the right side solely in twenty-three (26.4 per cent) and both in thirteen cases (14.9 per cent). The thrombotic process was limited to the arm veins in thirty-six cases (41.4 per cent) and to the neck veins in five (5.7 per cent). Both were included in forty-six cases (52.9 per cent). The case-vessel distribution in eighty-six cases is shown in Table III. In one case reported by Jolly[5] both upper extremities were involved but the exact venous distribution of the thrombi was not given. A clearer conception of the relative frequency of vessel involvement can be obtained from Figure 2. The subclavian veins alone were involved in sixteen cases (18.4 per cent), and the subclavian and jugular veins were involved concomitantly in eighteen cases (20.7 per cent).

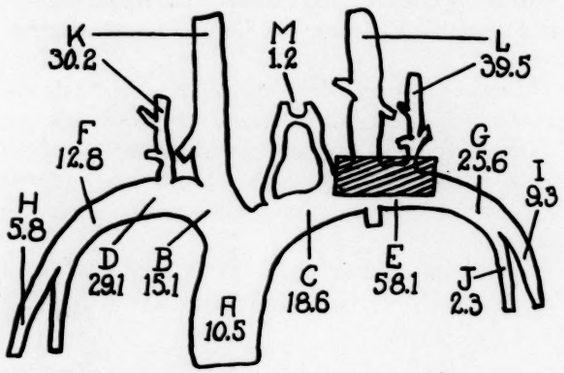


FIG. 2. Diagram showing the relative frequency of thrombosis of the individual veins in eighty-six patients given in per cent. A, superior vena cava; B, right innominate; C, left innominate; D, right subclavian; E, left subclavian; F, right axillary; G, left axillary; H, right brachial; I, left brachial; J, left basilic; K, right internal and external jugulars; L, left internal and external jugulars; M, inferior thyroids. The hatched area indicates the most common starting points of the thrombotic process.

In the thirteen cases reported by Sladen and Winternitz[17] the right upper extremity was more frequently involved than the left but in the present larger series there is a decided left-sided preponderance.

In those cases in which more than one vein was involved the most common combination was the continuous involvement of the left innominate, internal and external jugulars, subclavian and axillary veins.

The superior vena cava was wholly or partly involved in nine cases (10.5 per cent). Seven of these patients came to autopsy. Two patients developed a collateral circulation and improved sufficiently to be discharged from the hospital.

ONSET OF THROMBOSIS

The onset of venous occlusion was described as acute in fifty-one cases and gradual in six cases. It was not given in thirty cases. The exact definition of the terms "acute" and "chronic" was not always clear. The former usually implied a rapid development of the lesion over a period

varying between twelve hours and two days. The latter implied a slower, insidious process developing over a period of from five to eight days. In cases of massive anasarca the venous obstruction did not always present a clear-cut clinical picture. In the large majority of patients the thrombosis occurred during hospitalization or shortly before.

SYMPTOMATOLOGY

The signs and symptoms of venous occlusion of the upper extremity have been fully described elsewhere[4,30] and will be given only briefly here. Pain and edema were usually the first and most striking findings. In the sixty cases in which pain was specifically mentioned it was present and marked in forty-seven and absent in thirteen. Tenderness was noted in twelve cases. Edema was prominent in all cases and was usually brawny in character. It frequently spread to the anterior superior thorax and face. The thrombosed veins were described as being tender and "cord-like" in forty-five cases. Other conditions such as weakness, limitation of motion, superficial venous dilatation, mottling of the skin, cyanosis, numbness, coldness, stiffness, tightness and easy fatiguability were common. In some patients the signs and symptoms first presented in the arm and spread upward to involve the neck; in others, the reverse process was the rule.

A comparison of the clinical picture of this condition with that of primary (or effort) venous thrombosis reveals several interesting and important differences. These are listed in Table IV.

COMPLICATIONS AND PROGNOSIS

The most striking and serious complication was pulmonary infarction. It was present in thirty-six cases, absent in eighteen and not mentioned in thirty-three. The majority of the fifty-four patients in whom this complication was specifically mentioned came to autopsy. Ten of the thirty-six patients with pulmonary infarction had thrombi in the right side of the heart. Upon considering other possible sources of embolization, in only six cases was venous thrombosis mentioned as being present in the lower extremities and elsewhere. The femoral veins were involved in two cases, the iliac veins in three cases. In one patient the prostatic and spermatic plexuses contained thrombi.

The pulmonary embolus was fatal in thirty cases. In the remaining six patients it was believed that this complication markedly aggravated the already serious cardiac condition.

Sixty-five patients died at the time of the development of the venous thrombosis or shortly thereafter. The majority of these deaths were on a cardiac basis. Slight residual edema and limitation of use of the extremity were common in the twenty-two patients who survived.

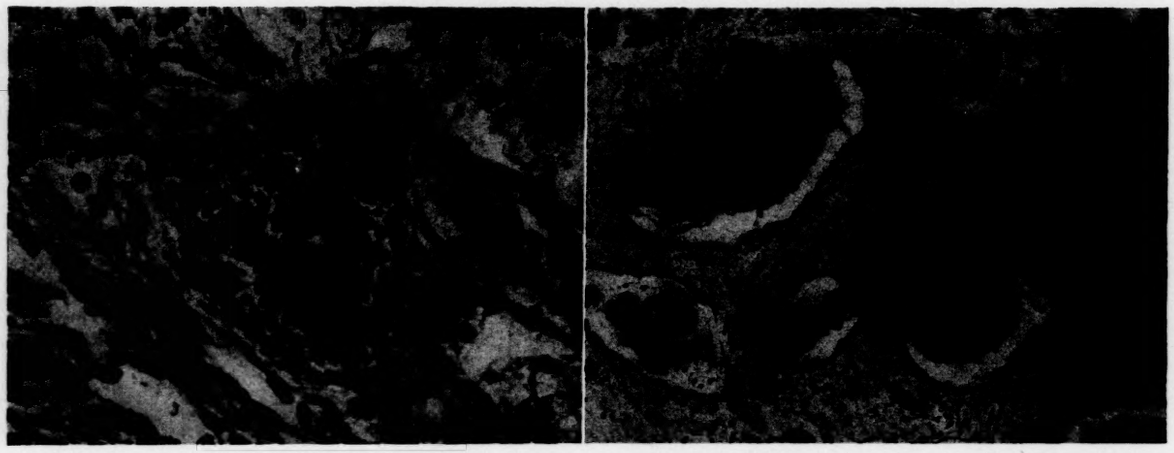
TABLE IV

A COMPARISON OF THE IMPORTANT DIFFERENTIAL POINTS OF VENOUS THROMBOSIS COMPLICATING HEART DISEASE AND EFFORT THROMBOSIS

Venous Thrombosis Complicating Heart Disease	Effort Thrombosis
Pain frequent and severe	Pain not common
Slight fever present	No febrile reaction
Marked constitutional reaction	No constitutional reaction
Left side more frequently involved	Right side usual site
Arm and neck most frequently included in process	Process usually limited to arm
More common in females	More common in males
No history of trauma	History of strain or injury present in most cases
Found more frequently in middle age	More common in young people
Pulmonary embolism frequent complication	Pulmonary embolism very rare
Prognosis as to life poor	Prognosis as to life good

The fact that only five cases of this series showed venous thrombosis of the lower extremities cannot be considered significant. We know from experience that this complication occurs much more frequently in heart disease than these figures indicate. The probable explanation is contained in the following factors: (1) the frequent difficulty encountered in making the diagnosis in a patient with marked dependent edema, (2) the failure to examine the legs at a routine autopsy to prevent unnecessary maiming of the body and (3) the failure to recognize the frequency and importance of this condition until relatively recently.

Sufficient evidence, however, has been presented, particularly in the cases reported since the time of Welch, that pulmonary embolism is an important and dire complication of venous thrombosis of the upper extremity and neck. In the fifty-nine cases collected by Sladen and Winternitz[17] pulmonary infarction occurred and was fatal in twenty-one patients. It occurred in nine of Veal and Hussey's[4] sixteen cases and was fatal in seven. Five of these patients came to autopsy, and in four the only source of embolism found was the thrombus in the subclavian and axillary veins.



3 4

FIG. 3. Photomicrograph of a section of vein wall from Case III showing an example of marked distention of a vas venarum by red blood cells; × 500.

FIG. 4. Photomicrograph of a section of vein wall from Case II showing varying sized thrombi within dilated vasa venarum; × 130.

PATHOLOGY

In those cases in which gross and microscopic descriptions were given the findings were essentially similar. All thrombi were of the mixed variety and all were firmly adherent to the vessel wall at at least one point. At the point of attachment they were gray or white in color and firm in consistency. This was presumed to be the site of origin. The remainder of the clot was grayish-red in color and somewhat more friable, a finding which is consistent with the high percentage of pulmonary emboli.

The most common sites of origin of the thrombi (Fig. 2) were the left internal and external jugular veins near their junction with the subclavian vein, the left innominate vein and the left subclavian vein near the entrance of the jugular veins. This finding has been previously noted and has stimulated much experimental work. Eberth and Schimmelbusch[34,35] first observed the tendency of platelets to accumulate at the meeting place of veins. Silberberg[36] citing Mantegassa and Zahn states that blood cells, in the formation of thrombi, attach to the vascular wall particularly at the site of branching. Hirschlaff[9] was of the opinion that clotting was promoted in areas where large valves are located and where two large veins meet at a sharp angle and produce marked eddying. This was also pointed out by Poynton.[15] Aschoff[37] and Beneke[38] found that irregularities in the blood current lead to the agglutination of the cellular elements.

On microscopic examination all of the cellular elements of the blood in addition to fibrin were found in the thrombus. Various stages of organization were present, depending upon the age of the lesion. Plasma cells and lymphocytes were frequently noted in the vein wall. In only one case (Welch's[16] Case I) were bacteria seen in the sections taken. As positive cultures were obtained from the thrombi in only two cases and as it is now known that the presence of a thrombus *per se* may incite an inflammatory reaction in the vessel wall, Welch's dictum that nearly every case of venous thrombosis is preceded by infection seems no longer to be valid. Many of the thrombi had undergone puriform liquefaction. This is now attributed to the release of enzymes.[36] Recanalization of the thrombus was not uncommon.

In three cases (those of Baldwin[13] and Cases II and III reported here) phlebosclerosis was present. No other evidence of previous disease was noted. Six cases (four from this center and those of Perry et al.[27] and Esselborn and Janchar[32]) showed marked dilatation of the vasa venarum. In four cases many were packed with red blood cells. (Fig. 3.) In a fifth case (Case II) they contained varying-sized thrombi. (Fig. 4.) These were composed of platelets, fibrin, white blood cells and occasional red blood cells. Several had been completely replaced by connective tissue. In others the stage of organization had progressed far beyond that of the large thrombus in the parent lumen. Perry and his

associates noted collections of spindle cells resembling Aschoff bodies surrounding the nutrient vessels.

ETIOLOGY

The theories offered to explain the etiology of venous thrombosis occurring in the upper extremities as a complication of heart disease have been legion. They have been thoroughly reviewed by both Welch[16] and Sladen and Winternitz,[17] so will be listed only briefly here. At various times such conditions as cardiac cachexia, anatomic peculiarities of the venous system (especially the longer and more oblique left brachiocephalic trunk), stagnation of venous blood, cardiac decompensation, infection and acute rheumatic fever have been considered important. Several authors, notably Baldwin,[13] believed that a combination of several of these factors was necessary.

It has now become almost universally accepted[39–43] that three factors are relevant to the formation of a thrombus within a vein. These factors are: (1) alterations in the rate of blood flow; (2) alterations in the quality or quantity of blood constituents and (3) alterations of the endothelial coats of veins. O'Neil is of the opinion that an imbalance of any two of them is sufficient to produce a spontaneous thrombosis. This observation, however, is not accepted by all authors.

It has been clearly shown that the complete stoppage of blood flow alone is not sufficient to cause thrombosis. As early as 1771 Hewson[44] demonstrated that blood remains liquid for a long period of time between ligatures in a vein segment. This was later confirmed by Thachrah.[45]

If the blood flow is too strong, conditions are not suitable for the formation of a thrombus. This is true, possibly, because of two factors: (1) the force of the current pushes the first platelet deposits away from the vessel wall[36] and (2) there is a rapid dilution of the thromboplastin formed at the site of endothelial injury. The relatively infrequent occurrence of arterial thrombosis is further evidence of this.

The most favorable condition for thrombus formation, therefore, is a retardation or oscillation of the blood current.

There are many varied physical and chemical conditions that alter both the quantity and quality of the blood constituents. The most obvious and common variant to be found in this series of patients was the reduced oxygen tension. The frequency and degree of cyanosis noted supports this finding. Further support is gained from the work of Barcroft[46] who designated three types of anoxia: (1) stagnant, (2) anoxic and (3) anemic. In the stagnant type the arterial blood has a normal oxygen content but the oxygen content of the venous blood is reduced. In the anoxic type the oxygen content of both arterial and venous blood is reduced.[47] In moderate congestive failure stagnant anoxia alone is present. In severe failure, with pulmonary edema, both the stagnant and anoxic types are found.[48] Therefore, in the absence of such conditions as chronic pulmonary disease, anemia, etc., the degree of anoxia parallels the degree of congestive failure. The exact incidence of other conditions that would interfere with the normal oxygenation of the blood in this series of patients is not known, but even if present they would serve only to further reduce oxygen tension and emphasize the variation in this particular constituent of the blood.

O'Neil,[43] in an excellent study of the effects on the venous endothelium of alteration in blood flow through the vasa venarum, made several interesting and pertinent observations. In one group of experimental animals he dissected segments of vein free from all surrounding tissue. These segments measured from 3 to 12 cm. In the process of dissection all vessels directly continuous with the vasa venarum were purposely destroyed. To insure isolation a rubber dam was loosely sutured about the segment. With the blood flow through the vein lumen unaltered the isolated section was allowed to remain *in situ* for periods varying from three to forty-eight hours. The isolated portion of vein was then removed, stained with a 1:250 silver nitrate solution and examined grossly and microscopically. In vein segments isolated for six hours focal areas of endothelial destruction and desquamation were noted. After thirteen and one-half hours the desquamated area was much larger. In those sections isolated twenty-three hours only a few endothelial cells remained intact. When the experiment was continued for forty hours, the inner surface of the vein was completely devoid of endothelium and a small adherent clot was present. Reduction of the diameter of the vein lumen by as much as 50 to 60 per cent was noted in experiments conducted longer than twelve hours. This change

was attributed to the tonic contraction of the circular muscles. As a result the minute volume of blood flow was reduced about 65 to 75 per cent, and the velocity of the blood flow was proportionally increased. This increase in velocity explained the absence of thrombus formation in some animals even though the endothelium was destroyed, and the blood was in contact with the roughened, "raw" muscular tissue—a tissue well known for its ability to produce thromboplastin.

In a second group of experimental animals slowing of the blood stream was produced by the use of special clamps. The blood supply to the vasa venarum was allowed to remain intact. The femoral and external jugular veins were used, and the clamps were left in place for periods ranging from nine to seventy-five hours. After nine hours the endothelium appeared granular and areas of focal desquamation were noted. A thrombus not attached to the vein wall was present in the lumen. After twenty-nine hours the damage to the endothelium was more marked and a non-adherent clot also formed in the lumen. Partial clamping for seventy-five hours led to still more marked changes. However, at no time was the destruction of the endothelium as marked as when the vasa venarum were isolated. In a series of nine experiments in which both vasa venarum were isolated and the circulation slowed for varying lengths of time, thrombosis repeatedly occurred in four instances. The experimental period for these four animals was twenty-four, twenty-five, thirty and fifty hours, respectively. On only one occasion did a thrombus form when these conditions existed for less than twenty-four hours.

As early as 1886 Eberth and Schimmelbusch[35] observed that platelets will be deposited and a white thrombus will form at the site of damage in a blood vessel wall. Further observations of this same process were later made by Murray and his associates.[49]

In a patient with severe congestive failure, and especially one with mitral valvular disease, two of the three relevant factors for the formation of a venous thrombus are present. The alteration in the rate of blood flow is one of slowing, and the alteration of the blood constituents is a reduction in the concentration of oxygen. The presence of the third factor, however, is more important than the other two.

As previous work on the anatomic distribution of the vasa venarum has been limited, O'Neil,[43] as a preliminary step to his experiments, undertook the problem of demonstrating their pattern. He found that an arteriolar branch from a neighboring artery entered the adventitial coat of the vein and divided and sub-divided many times to form a rich capillary network within the vein wall. This extensive plexus was eventually drained by two separate venous systems. In one system the venules emptied directly into the parent lumen. In the other they emerged from the adventitia and emptied into some other vein in the vicinity or into the parent lumen at some more proximal site. Because of the limitations of his staining technic he was unable clearly to show the penetration of the vasa venarum into the media and intima. There seems to be little doubt, however, that penetration does occur. The readiness with which a thrombus in the parent lumen organizes is good evidence of this.

It has been shown repeatedly that in severe congestive failure there is a marked increase in the circulating blood volume. There is also a corresponding rise in venous blood pressure. As the arterial pressure is usually maintained until the terminal episode there is a meeting of these two forces at the capillary level. This loss of normal pressure differential superimposed upon the increase in blood volume results in a vast pooling of blood in the capillary network. This pooling occurs in the capillaries of the vein wall as well as in those of other organs. The prolongation of the circulation time, so frequently seen in cardiac patients, offers clinical support to this observation. It was also illustrated anatomically in at least four patients from this series. As noted previously, sections from these cases showed not only marked dilatation of the vasa venarum in the vicinity of the thrombus but large accumulations of red blood cells present in these dilated vessels.

The most common site of origin of the thrombi in this series was at the junction of large veins. At this point the eddying of the blood (Wirbelbewegung of von Recklinghausen) is most marked. As a result the pressure here is somewhat higher than that found generally in the venous system. This increase is transmitted distally through those venules of the vasa venarum that empty into the parent lumen in this area. The venous return from the vein wall is thereby impaired. In the normal circulatory system this phenomenon probably has very little significant effect. In a patient with already severe congestive failure it further contributes

toward stagnation of the blood in the mural capillary system.

Both Hirschlaff[9] and von Recklinghausen[50] emphasized the importance of eddying of the blood in the vicinity of the thrombus formation.

This pooled blood is already poor in oxygen content. Continued stagnation permits further utilization of the oxygen by the tissues. The blood oxygen saturation is consequently further reduced and, with limited opportunity for replenishment, a critical level is approached. When this condition exists within the capillary bed of the vein wall, one of the chief sources of oxygen supply to the endothelium is significantly impaired. The other possible source of endothelial oxygen supply is also impaired by the generalized alteration in the rate of flow, the localized eddying and the reduced oxygen concentration of the blood present in the parent lumen.

If a combination of these conditions persists over a long period of time and if they become sharply emphasized by a sudden increase in the severity of the failure, it is not unreasonable to assume, in the light of O'Neil's work, that endothelial injury will result. With this injury to the endothelium all three relevant conditions for the formation of a thrombus are then present. Platelets will adhere to the damaged surface, thromboplastin will be produced and, as shown by Eberth and Schimmelbusch[35] and Murray et al.,[49] thrombosis will occur.

It should again be noted here that four-fifths of the patients in the series were in congestive failure over a period ranging from several months to several years. It should also be noted again that all of the thromboses occurred just before or during a period of hospitalization for a marked and frequently a sudden increase in the severity of their cardiac complaints.

Further evidence accumulated from the analysis of this series of cases lends support to this theory as follows: (1) All thrombi were adherent to the vein wall at at least one point, (2) these were of the so-called white variety at the point of adherence, (3) with the exception of two cases, no evidence of infection was found, (4) mitral valvular disease was present in almost one-half of the cases, (5) there was no history of trauma given and (6) marked cyanosis was a frequent finding.

Much of the work cited above to explain the site of thrombosis could also be applied here to explain further the actual production of the thrombus. The tendency of platelets to accumulate at the meeting place of veins[34,35] and the promotion of agglutination of the cellular elements of the blood by current irregularities[37,38] are particularly pertinent observations.

In some instances, as in Case II reported herein, actual thrombi may form in the vasa venarum. Their etiology and pathogenesis could also be explained by the mechanism described above. If they completely occlude the vasa venarum, endothelial injury, as O'Neil has shown, would result and thrombosis could occur. However, in this particular case even though some of the thrombi had undergone complete organization, it cannot be said with certainty that their formation preceded that of the main thrombus in the parent lumen. Further study of this possibility is indicated.

The theory outlined above could be applied even more easily to venous thrombosis of the lower extremities complicating heart disease. The return of blood from the upper extremities is greatly aided by the effect of gravity. It is also aided by continuous muscular activity. Even though a patient is confined to bed he usually continues the free use of his arms. The effect of gravity opposes the venous return from the lower extremities. The efficiency of the circulation is strongly dependent, therefore, upon the muscular activity of the legs. If bed rest is utilized as a therapeutic measure, this latter mechanism is greatly impaired. With the added effects of gravity and the reduction in muscular activity, venous thrombosis of the lower extremities could therefore be much more easily initiated.

COMMENT

Thrombosis of the veins of the upper extremity and neck is a serious but not a common complication of cardiac failure. It occurs more frequently in females than males. The ratio is 2.54 to 1. There are apparently two periods in life during which it is more likely to occur. These are the third and the fifth decades. The types of inciting cardiac diseases are varied. The most common type is rheumatic heart disease. Hypertensive cardiovascular disease is second. The apparent common denominator is the inability of the myocardium to maintain an adequate circulation. The presence of organic mitral valvular disease probably contributes significantly to the production of the lesion. Secondary anoxia is also important. The thrombi occur predominantly on the left side.

All of the veins of the upper extremity and lower neck may be involved in various combinations. The subclavian vein is the most frequently occluded. The most frequent combination is the subclavian and lower jugular veins. Several theories to explain the site of involvement have been cited. None appears to be completely adequate. The onset of thrombosis is usually acute and the clinical picture is striking. Pain and edema appear initially and are accompanied by a moderate to severe constitutional reaction. The thrombosed veins are tender and "cord-like" and can usually be palpated. The process may spread to involve the neighboring veins, and the extension is most frequently in the direction of the blood flow. The accompanying signs and symptoms are those to be expected following venous occlusion from any cause. The most serious complication is pulmonary embolism with infarction. It may be fatal in a large percentage of cases. In those patients who survive marked aggravation of the cardiac condition may be expected. The prognosis is far from favorable and death usually results from the cardiac disease. Residual edema following limited use of the involved extremity is common in the non-fatal cases. This condition differs significantly as to age, sex, etiology, site of involvement, constitutional reaction and prognosis from the so-called "primary or effort" thrombosis.

CASE REPORTS

CASE 1. C. O'K. (autopsy No. UA 43-37), a forty-six year old white male, was admitted to the University Hospital three times between January 1, 1943, and April 26, 1943. His first admission was for frequent headaches, nocturnal dyspnea, blurring of vision, nocturia and progressive ankle edema. On physical examination the blood pressure was 210/138. The temperature, pulse and respirations were normal. The fundi showed evidence of marked hypertensive retinopathy. The heart was enlarged to the left. A complete clinical and laboratory work-up revealed a moderately advanced loss of kidney function and early cardiac failure. He was digitalized and discharged slightly improved after sixteen days in the hospital.

One month later he was readmitted because of frequent episodes of dyspnea, recurrence of occipital headaches, ankle edema and gross hematuria. At this time the blood pressure was 200/130. Kidney function tests showed further damage. He was discharged after four days.

His final admission occurred nine days later when he lapsed into coma following a generalized convulsion. The blood pressure was 240/130, pulse 120 and respirations 28. Serum NPN was 66 mg. per cent. Following admission his condition showed little change. On his fourth hospital day a pitting edema of both arms suddenly appeared. It was more marked on the left and extended from the antecubital space to the axilla. Redness and ecchymosis were noted. Pain was present over the entire upper arm. On the following day the signs and symptoms in the left arm became more acute. The edema of the right arm subsided slowly. The temperature remained around 101°F.

In spite of digitalis, diuretics and general cardiac measures his condition became more critical. Five days before death the first signs of pulmonary infarction were noted. He expired on May 25, 1943. The final clinical diagnosis was: malignant hypertension, hypertensive heart failure, thrombosis of the left subclavian vein and pulmonary infarction.

Autopsy was performed five hours postmortem. About 700 cc. of free fluid were found in each pleural space. A fibrino-purulent exudate covered both pleural surfaces. The posterior superior mediastinum was moderately edematous. The left subclavian vein was completely occluded by a reddish-brown thrombus. At one point it was firmly adherent to the intimal surface, and in this area it was gray in color. The right subclavian vein contained no evidence of thrombosis. The heart weighed 620 gm. and its left ventricle was markedly hypertrophied. In each auricular appendage a small, rounded, yellow-brown, friable thrombus was found. The left lung weighed 530 gm., the right lung weighed 860 gm. Both contained areas of infarction. The kidneys were small with pitted surfaces. Infarcts were also present in the spleen. The brain weighed 1,300 gm. and was without gross lesion.

Microscopically, the thrombus in the subclavian vein was of the mixed variety. The underlying endothelium was destroyed. Early evidence of organization was present. The vein wall in the vicinity of the thrombus contained both acute and chronic inflammatory cells. The vasa venarum were dilated and contained many erythrocytes. No bacteria were seen on specially stained sections. Hypertrophy and

Zenker's degeneration of the myocardium were present. The kidney contained marked arteriolar nephrosclerosis involving interlobular and some preglomerular vessels. Arteriosclerosis with calcification was present in the cerebral vessels.

CASE II. V. S. (autopsy No. A46-116), a fifty-eight year old white, married female, was admitted to the Syracuse Memorial Hospital on May 5, 1946, with the chief complaint of progressive pain and swelling of the right arm of four days' duration. She had been a known hypertensive with an average blood pressure of 200/100 for many years. Four to five years before admission she had first noticed gradual diminution of her cardiac reserve. In December, 1943, she developed a severe thyrotoxicosis and cardiac failure followed. Her cardiac status improved after thyroidectomy but the improvement was transient. She was then digitalized because of dyspnea, palpitations, ankle edema, orthopnea and paroxysmal nocturnal dyspnea. Four days before admission she noted the sudden onset of soreness in the right anterior triangle of the neck and marked pain and swelling of the right arm. There was no history of trauma. Her past history and system review were non-contributory. On admission her temperature was 101°F., pulse 120, respirations 36 and blood pressure 200/100. A tender, inflamed, pencil-like swelling was found in the right anterior neck. The heart was enlarged to the left; heart sounds were of fair quality. A distant systolic murmur was heard over the entire precordium. Crepitant rales were present at both lung bases. The right arm was tender and swollen to about twice its normal size by a brawny edema. Thrombosed veins could not be palpated. The left arm was also tender and painful on motion. It was only slightly swollen. Laboratory work-up revealed a normal red blood cell count, a leukocytosis and a 2 to 4 plus albumin in the urine. Blood cultures yielded no growth. X-ray examinations showed left ventricular enlargement and later pulmonary infarcts. An electrocardiographic tracing indicated only digitalis effects. She was placed on a cardiac regimen, antibiotics and elevation of the right arm. During the first four days of hospitalization she experienced two episodes of pulmonary infarction and was placed on anticoagulant therapy. On the sixth hospital day her left arm, neck and face became markedly swollen. The pencil-like swelling in the right neck extended superiorly to the mandible. Her temperature remained around 100°F. Edema became more marked. On the thirteenth hospital day signs of cerebral infarction appeared. Three days later a pattern of venous dilatation was noted over the anterior thorax. She lapsed into coma and expired on May 23, 1946, her eighteenth hospital day.

Autopsy was performed five hours postmortem. The lumen of the superior vena cava was almost completely occluded by a partially adherent, pink, friable thrombus. It extended distally into both innominate veins, both subclavian veins and into the right external jugular vein. That portion of the thrombus in the jugular vein was gray in color, much more firm in consistency and markedly adherent to the vessel wall. The heart weighed 450 gm. The left ventricle was greatly hypertrophied and the right auricle was dilated. Fibrosis of the myocardium was noted grossly. The left lung weighed 750 gm., the right lung weighed 500 gm. Both contained several small infarcts. The superior mediastinal tissue was somewhat indurated. The brain weighed 1,250 gm. and its right parietal lobe contained an area of necrosis resembling an infarct.

Microscopically, the thrombus was composed of red and white blood cells, thrombocytes and fibrin. Early organization was present. Many lymphocytes and plasma cells were dispersed throughout the vein wall. The vasa venarum were dilated. Some contained red blood cells and others were occluded by varying sized thrombi. These were composed of white blood cells, thrombocytes, fibrin and an occasional red blood cell. They had undergone various degrees of organization and some were completely replaced by fibrous tissue. No evidence of bacteria was found. A moderate increase in fibrous stroma was present in the myocardium. Some arteriolar intimal thickening was also noted. The pulmonary infarcts were partly organized.

CASE III. M. St. L. (autopsy No. A47-45), a sixty-one year old, white female, entered the University Hospital on February 22, 1947, with the chief complaint of swollen ankles of six months' duration, progress worse. She was in her usual good health until about two years before admission. At that time she first noted ankle edema, dyspnea and orthopnea. Six months before admission she was digitalized because of the increasing severity of these complaints. Four weeks before admission, while on bed rest, a large amount of fluid accumulated in her peritoneal cavity. Just prior to admission a marked brawny edematous swelling of the left arm appeared

suddenly. It extended to the axilla and was accompanied by moderate discomfort and limitation of motion. The right arm was not involved. There had been no history of hypertension. Her past history and system review were otherwise non-contributory. On admission her temperature was 99.6°F., pulse 150, respirations 40 and blood pressure 120/80. She was orthopneic and cyanotic. Distention of the jugular veins was prominent. The heart was enlarged to the left and the apical beat was diffuse. A loud blowing systolic murmur was heard over the entire precordium. Crepitant rales were present in both lung fields. The abdomen was distended by a massive ascites. A 4 plus pitting edema of the legs and a 2 plus pitting edema of the left arm were present. The superficial veins of the arm were markedly distended and collapsed only on vertical elevation. No pain or tenderness was noted. The right arm was negative. The red and white blood counts and urinalysis were within normal limits. The blood sugar was 168 mg. per cent, the serum NPN 71 mg. per cent. An electrocardiographic tracing was interpreted as showing right heart strain. She was placed on a cardiac regimen and a paracentesis was done. Approximately 2,450 cc. of serosanguineous fluid were removed. Shortly thereafter she developed auricular flutter that failed to respond to quinidine. Dyspnea and cyanosis were marked. Serial electrocardiograms showed an irregular shift between auricular flutter and fibrillation. The lower right arm suddenly became edematous and resembled the left arm in appearance. Her condition remained critical in spite of all therapeutic efforts and she expired on March 1, 1947.

Autopsy was performed two hours postmortem. The peritoneal cavity contained 2,000 cc. of serosanguineous fluid. Dense fibrous adhesions enclosed the liver. Each pleural cavity contained about 800 cc. of fluid resembling that found in the abdomen. The heart weighed 390 gm. There was a marked right-sided dilatation. The tricuspid ring was enlarged and the valves were incompetent. A small thrombus was present in the right auricular appendage. Coronary artery atherosclerotic degeneration was marked. The right lung weighed 375 gm., the left lung 350 gm. Both lower lobes were atelectatic. Many thrombi were present in the branches of the pulmonary artery but no areas of infarction were present. Both axillary veins were occluded by thrombi. Each was firm, gray and adherent in some areas and deep red and friable in others. The liver weighed 1,100 gm. and contained areas of scarring and calcification.

Microscopically, both axillary vein walls were thin. They contained many lymphocytes and fewer plasma cells. The vasa venarum were dilated and some were packed with red blood cells. The thrombus was of the mixed variety. Definite invasion by capillaries and fibroblasts was present. Slight fibrosis of the myocardium was noted. Organization was advanced in some of the pulmonary artery thrombi but absent in the auricular thrombus. Heavy strands of scar tissue were seen in sections of the liver.

Case iv. V. F. (autopsy No. A47-99), a twenty-one year old, white female, was admitted to the Syracuse General Hospital on March 10, 1947, with the chief complaint of swelling of both ankles and legs of two months' duration, progress worse. At the time of admission she was in approximately the twenty-sixth week of her first pregnancy. Two months before admission she had first noted swelling of her legs and ankles. There were no symptoms of cardiac insufficiency at that time. There was no known history of scarlet fever, rheumatic fever or kidney disease. At the time of admission her temperature was 98°F., pulse 60, respirations 20, blood pressure 180/120 and weight 137 pounds (normal weight 115 pounds). Funduscopic examination was negative. Heart and lungs were within normal limits. There was a 4 plus pitting edema of the feet, legs and thighs bilaterally. Neither of the upper extremities was involved. The red and white blood cell counts were within normal limits. A urinalysis showed a specific gravity of 1.029, a 4 plus protein, a 1 plus sugar and white blood cells, red blood cells and casts were seen microscopically. The serum NPN was 30 mg. per cent. The blood serology was negative. She was given supportive therapy without improvement. On her eighth hospital day she developed cardiac failure with pulmonary edema and was digitalized. Two days later she spontaneously delivered a stillborn fetus. Antibiotics were started. On her eleventh hospital day her serum NPN rose to 138 mg. per cent. Within the following week it gradually returned to normal. In spite of vigorous therapy her cardiac status failed to improve significantly. Fourteen days before death a hard, pitting edema suddenly appeared in her left upper extremity and extended to the mid-upper arm. She complained of discomfort but no actual pain. It was treated

with elevation and penicillin. One week later she first coughed up mucous material containing bright red blood. At this time a bilateral hydrothorax and ascites were first noted. A culture of the thoracentesis fluid yielded no growth. Electrocardiographic tracings were interpreted as showing myocardial degeneration. Following a relentless downhill course she expired on May 10, 1947.

Autopsy was performed four hours postmortem. The peritoneal cavity contained 1,000 cc. of straw colored fluid. The right diaphragm was markedly depressed. Each pleural space contained up to 200 cc. of fluid grossly resembling that found in the abdomen. The heart weighed approximately 430 gm. and was both dilated and hypertrophied bilaterally. Both ventricular cavities contained small mural thrombi. The right lung weighed 450 gm., the left lung 180 gm. Branches of both pulmonary arteries contained varying-sized emboli. Bilateral areas of pulmonary infarction were present. A large red-brown friable thrombus completely occluded the left axillary vein. It was firmly adherent in its proximal portion and in this area was gray in color. Several large segments of thrombus were expressed from the right common iliac vein. The remainder of the vascular system was negative.

Microscopically, the axillary vein showed no evidence of previous disease. The cellular reaction within its wall was minimal. The vasa venarum were dilated and packed with red blood cells. The thrombus contained all of the cellular elements of the blood and organization was well established. The myocardial fibers did not stain deeply. Organization was present in the ventricular thrombi. The glomeruli of the kidney were very cellular and bloodless. Sections stained with Masson's trichrome stain showed early proliferation and scarring of the capsule.

SUMMARY

Eighty-three cases of thrombosis of the veins of the upper extremities, as a complication of heart failure, have been collected from a review of the literature. Four additional cases are reported.

These have been analyzed to show the incidence of age, sex and race of the patient, the type of cardiac lesion, the degree and duration of heart failure, the location and type of onset of the thrombosis, symptomatology, complications and prognosis. A possible mechanism of etiology and pathogenesis is described.

REFERENCES

1. Matas, R. Primary thrombosis of the axillary vein caused by strain. *Am. J. Surg.*, 24: 642, 1934.
2. Bouchut, E. Mémoire sur la coagulation du sang veineux dans la cachexies et dans les maladies chroniques. *Gaz. méd. de Paris*, 13: 245, 1845.
3. Barker, N. W., Nygaard, K. K., Walters, W. and Priestly, J. T. A statistical study of postoperative venous thrombosis and pulmonary embolism. IV. Location of thrombus: relation of thrombosis to embolism. *Proc. Staff Meet., Mayo Clin.*, 16: 33, 1941.
4. Veal, J. R. and Hussey, H. H. Thrombosis of the subclavian and axillary veins. *Am. Heart J.*, 25: 355, 1943.
5. Jolly, J. F. G. De la phlegmasia alba dolens. Thèse de Paris, No. 43, 1861.
6. Ramirez, L. De l'oblitération de veines jugulaires comme complication des affections cardiaques. *Gaz. méd. de Paris*, 22: 716, 1867.
7. Duguet, J. B. De l'apoplexie pulmonaire. Thèse de Concours. Paris, 1872. P. Asselin.
8. Ormerod, J. A. Thrombosis of veins of neck. *Tr. Path. Soc. London*, 40: 75, 1889.
9. Hirschlaff, W. Beitrag zur Lehre und Casuistik von der Thrombose der Vena jugularis interna, externa, und subclavia. Inaug. Diss. Berlin, 1893.
10. Huchard, H. Cachexie cardiaque et thromboses veineuses. *Rev. gén. de clin. et de thérap.*, 11: 787, 1897.
11. Gatay, L. Contribution à l'étude de la phlébite rhumatismale. Thèse de Paris, No. 82, 1895.
12. Meslay, R. F. Thrombose spontanée de veines sous-clavière, axillaire et humérale droites chez un enfant atteinte de lésion cardiaque d'origine rhumatismale. *Rev. mens. d. mal. de l'enf.*, 13: 559, 1895.
13. Baldwin, H. Thrombosis of the jugular veins. *J. A. M. A.*, 29: 371, 1897.
14. Nicolle, C. and Robineau, M. Phlébite de la veine jugulaire externa chez une malade atteinte d'endocardite mitral. *Normandie méd.*, 12: 68, 1897.
15. Poynton, E. J. Three cases of extensive venous thrombosis associated with severe rheumatic carditis; necropsies. *Lancet*, 2: 206, 1898.
16. Welch, W. H. Venous thrombosis in cardiac disease. *Tr. A. Am. Physicians*, 15: 441, 1900.
17. Sladen, F. J. and Winternitz, M. C. Venous thrombosis during myocardial insufficiency. *Johns Hopkins Hosp. Rep.*, 17: 511, 1916.
18. Ford, W. W. Venous thrombosis in heart disease. *Philadelphia, M. J.*, 6: 960, 1900.
19. MacGregor, J. A. Peripheral venous thrombosis in cardiac disease, with report of a case. *Am. Med.*, 1: 353, 1901.
20. White, W. H. On two cases of venous thrombosis in heart disease. *Clin J.*, 20: 297, 1902.
21. Favier, J. Des thromboses veineuses au cours des cardiopathies. Thèse de Lyon, 1903.
22. Desquiens, L. Thrombose du tronc veineux brachio-cephalique droit chez une cardiaque. *Bull. Soc. anat. de Paris*, 79: 429, 1904.

23. Desquiens, L. Phlegmatia alba dolens du membre supérieur chez les asystoliques. Thèse de Paris, No. 37, 1906.
24. Lacombe, M. Thrombose veineuse au cours d'une asystolié. *Rev. gén. de clin. et de thérap.*, 18: 358, 1904.
25. Collet, M. and Curtil, A. Un cas de thrombose jugulosous-clavière chez une cardiaque. *Clinique, Paris*, 4: 228, 1909.
26. Blumer, G. Report of four unusual cases of peripheral venous thrombosis. *Yale M. J.*, 15: 296, 1908–9.
27. Perry, C. B., Davis, O. C. M. and Schlesinger, B. Thrombophlebitis in acute rheumatism. *Lancet*, 2: 966, 1933.
28. Finley, D. E. Thrombosis complicating hyperthyroidism. *Brit. M. J.*, 2: 966, 1937.
29. Towers, J. R. H. and Oldfield, M. C. Thrombosis of subclavian vein complicating hyperthyroidism. *Brit. M. J.*, 1: 808, 1937.
30. Veal, J. R. Thrombosis of the axillary and subclavian veins. *Am. J. M. Sc.*, 200: 27, 1940.
31. De Bakey, M., Ochsner, A. and Smith, M. C. Primary thrombosis of the axillary vein. *New Orleans M. & S. J.*, 95: 62, 1942–3.
32. Esselborn, V. and Janchar, L. J. Propagating axillary and subclavian venous thrombosis with extension into the dural sinuses and intracerebral veins. *Ohio State M. J.*, 42: 739, 1946.
33. New York Heart Assoc. Inc. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, 4th ed., p. 73. New York, 1945. J. J. Little and Ives Co.
34. Eberth, J. C. and Schimmelbusch, C. Experimentelle Untersuchungen über Thrombose. *Fortschr. d. Med., Berlin*, 3: 379, 1885.
35. Eberth, J. C. and Schimmelbusch, C. Experimentelle Untersuchungen über Thrombose. *Fortschr. d. Med., Berlin*, 4: 115, 1886.
36. Silberberg, M. The causes and mechanism of thrombosis. *Physiol. Rev.*, 18: 197, 1938.
37. Aschoff, L. Thrombose und Sandbankbildung. *Beitr. z. path. Anat. u.z. allg. Path.*, 52: 205, 1912.
38. Beneke, R. Handbuch d. allg. Pathologie. By F. Marchand and L. Krehl. Vol. II, Chap. 2, p. 130. Leipzig, 1913. S. Hirzel.
39. Aschoff, L. Thrombose und Embolie. *Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch.*, 7: 11, 1934.
40. Aschoff, L. Ueber Thrombose und Embolie. *Wien klin. Wchnschr.*, 51: 1277, 1938.
41. Best, C. H. and Taylor, N. B. The Physiological Basis of Medical Practice, 5th ed., p. 123. Baltimore, 1950. The Williams and Wilkins Co.
42. Copley, A. L. and Stefko, P. L. Coagulation thrombi in segments of artery and vein in dogs and the genesis of thromboembolism. *Surg., Gynec. & Obst.*, 84: 451, 1947.
43. O'Neil, J. F. The effects on venous endothelium of alterations in blood flow through the vessels in the vein walls and the possible relation to thrombosis. *Ann. Surg.*, 126: 270, 1947.
44. Hewson, W. Experiments on the Blood. London, 1771. W. Bowyer and J. Nichols.
45. Thachrah, C. T. Inquiry into the Nature and the Properties of the Blood, 1st ed., p. 42. London, 1819.
46. Barcroft, J. Anoxemia. *Lancet*, 99: 485, 1920.
47. Fulton, J. F. Howell's Textbook of Physiology, 15th ed., p. 890. Philadelphia and London, 1947. W. B. Saunders Co.
48. Best, C. H. and Taylor, N. B. The Physiological Basis of Medical Practice, 3rd ed., p. 592. Baltimore, 1943. The Williams and Wilkins Co.
49. Murray, D. W. G., Jaques, L. B., Perreth, T. S. and Best, C. H. Heparin and the thrombosis of veins following injury. *Surgery*, 2: 163, 1937.
50. von Recklinghausen, F. D. Handb. d. allgem. Pathologie d. Kreislaufs u. d. Ernährung, vol. 43, p. 129. Stuttgart, 1883.

Pulmonary Infarction Complicating Thrombophlebitis of the Upper Extremity*

CLYDE E. TOMLIN, M.D.
Atlanta, Georgia

THE important relationship between thrombophlebitis occurring in the lower extremities and pulmonary embolism has received much emphasis during the past decade. It has been stated that 95 per cent of pulmonary emboli originate from thrombosis of the veins in the lower extremities.[1] Thrombophlebitis of the upper extremities, however, is usually considered a benign condition, and pulmonary embolism originating from this location is regarded as uncommon. It is the purpose of this paper to emphasize the serious nature of thrombophlebitis of the upper extremities in regard to the complication of pulmonary embolism by presenting in detail five cases with pulmonary embolism. We have also encountered eleven cases of phlebitis of the upper extremities in which pulmonary embolism did not occur. This latter group was studied with particular reference to the etiologic factors in thrombophlebitis of the arm and is not intended to indicate the percentage of cases complicated by pulmonary embolism. These patients have been observed over a three-year period from the medical services of Emory University Medical School at Lawson Veterans Administration Hospital and Grady Memorial Hospital.

CASE REPORTS

CASE 1. J. S., a sixty year old colored practical nurse, was admitted to Grady Memorial Hospital on November 27, 1948. Cough, sore throat and moderate dysphagia had been present for two months prior to admission. Her temperature had been as high as 102°F. She had expectorated white mucoid sputum streaked with dark brown material but there was no bright red blood present. She had not experienced pleuritic pain.

Two weeks before admission to the hospital the x-ray of the chest taken in the medical clinic revealed patchy consolidation throughout both lung fields and the right diaphragm was obscured. The patient failed to return the following day as she was advised to do. In her home she had been lifted by support of the axillas on several occasions, and ten days prior to admission she noted swelling of the entire right upper extremity.

In 1942 cervical biopsy had shown anaplastic carcinoma. She had been treated with radium but had not returned for examination. A barium enema five months prior to admission had shown a questionable rectal stricture. Three months prior to admission a benign mixed tumor of the right parotid gland had been removed.

On admission the patient's temperature was 102°F., pulse 120 per minute and blood pressure 140/90. The patient was an acutely ill, obese colored woman expectorating white mucus. There was a soft, tender mass in the region of the left parotid gland. The right pupil was smaller than the left and there was ptosis of the right eyelid. Dulness and numerous moist rales were present in both lung bases. The apex impulse was 11 cm. to the left of the mid-sternal line in the fifth anterior intercostal space. The cardiac rhythm was regular. Mitral systolic murmur, grade 2, was heard. The abdomen was normal to examination. The cervix uteri was not palpable. The uterus was irregular but there was no fixation of the organ. Rectal examination was normal. There was massive pitting edema of the right upper extremity and shoulder. A firm thrombus was palpable in the right axillary vein.

The blood Kahn was negative. The urine contained 2 plus albumin. The white blood cell count was 18,400, with 85 per cent segmented neutrophils, 3 per cent stab cells, 1 per cent juvenile cells and 11 per cent lymphocytes. Blood cultures were sterile. Sputum smears were negative for acid-fast bacilli.

* From the Department of Cardiology, Emory University School of Medicine, Atlanta, Ga.

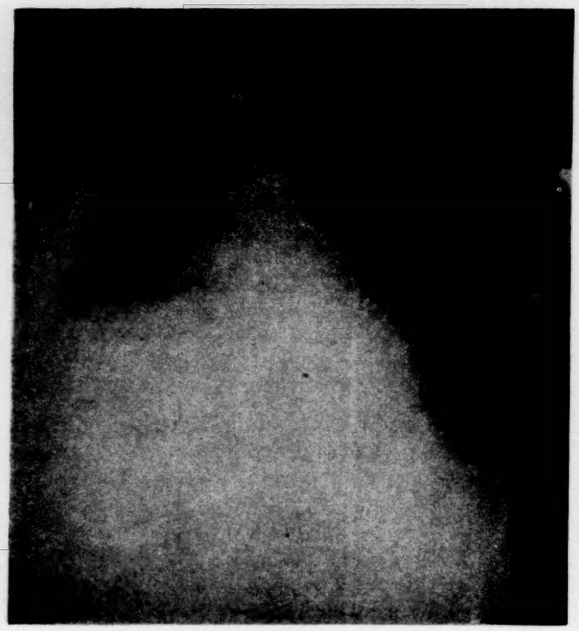


FIG. 1. Chest x-ray of Case I.

The initial impression was that the patient had obstruction of the veins at the base of the neck due to neoplasm, either secondary to the malignancy of the cervix or primary pulmonary neoplasm. On further evaluation it was apparent that the patient had thrombosis of the axillary vein with multiple pulmonary infarctions.

The chest x-ray on the day of admission revealed elevation of both diaphragms and patchy areas of consolidation in the right upper lobe and in the left mid-lung field, with lesser involvement of both lung bases. The findings were thought to be consistent with bronchopneumonia or multiple pulmonary infarctions. (Fig. 1.)

Throughout her hospitalization the patient had a toxic course. Her temperature ranged between 100° and 103°F. The dyspnea became more severe and she was too weak to take nourishment. She received penicillin, dicumarol and digitalis. On several occasions she experienced the sudden onset of marked dyspnea and sweating accompanied with the signs of shock. On December 9, 1948, she expired.

At postmortem bilateral pleural effusion was found, with multiple bilateral pulmonary infarctions. Antemortem thrombi were present in the medium-sized arteries of the left upper lobe. A firm thrombus was found in the right axillary vein extending into the subclavian vein. To this thrombus small soft blood clots were attached which resembled postmortem thrombi but which were difficult to separate from the adherent thrombus. The right brachial vein contained a thrombus which was firmly attached to the vein wall. There was no inflammatory reaction surrounding the veins. No thrombi were found in the pelvic veins or femoral veins. Microscopic examination demonstrated recanalization of the organized thrombus in the right axillary vein. No residual carcinoma of the cervix was present. The neck was not completely dissected but no evidence of parotid tumor was present in the base of the neck.

CASE II. G. W. B., a twenty-seven year old white male salesman, was admitted to Lawson Veterans Administration Hospital on May 18, 1950, with the chief complaint of hematuria, weakness and headache. The hematuria was first present in 1943, at which time the patient first knew he had hypertension.

On admission to the hospital the blood pressure was 270/180 in the upper extremities and 300/200 in the lower extremities. There was bilateral papilledema, many old exudates, extensive fundal hemorrhages and marked arteriolar constriction. There was slight cardiac enlargement to the left. The cardiac rhythm was regular. The aortic second sound was tambour. There was marked tenderness in both upper quadrants and in the costovertebral angles. The kidneys were not palpable.

The hemoglobin was 13.9 gm. per cent. Hematocrit was 44 mm. The white blood cell count was 12,100 with 73 per cent neutrophils, 20 per cent lymphocytes, 6 per cent eosinophils and 1 per cent basophils. Non-protein nitrogen was 40 mg. per cent. Phenolsulfonphthalein excretion test revealed 45 per cent in one hour. There were innumerable red blood corpuscles present in the urine. Urine cultures were negative.

The flat plate of the abdomen, intravenous pyelograms and retrograde pyelograms were normal. Fluoroscopy of the chest on May 22nd did not reveal any abnormality of the heart, lungs or great vessels. The electrocardiogram showed changes of left ventricular strain. Benzodioxan test was negative. It was believed that his diagnosis lay between chronic glomerulonephritis and arteriolar nephrosclerosis.

On June 1st, while the patient was on leave from the hospital, he was stung by a wasp on the right forearm. Four days later a localized area of cellulitis appeared at the right elbow above the site of the sting. A definite thrombus could not be palpated in this tender, indurated

area. On June 13th severe pleuritic pain developed in the base of the right lung and the next day he experienced the same type of pain in the left base. X-ray of the chest on this date was normal. The following day x-ray demonstrated obliteration of the left costophrenic angle with density in the left base. On June 15th a pleural friction rub was present in the left base and for the first time a large thrombus was evident just above the right elbow in the basilic vein. He was started on heparin and his clotting time was satisfactorily prolonged. However, he continued to have small hemoptyses and on June 21st x-ray of the chest showed changes of further infarction in both lung bases, more marked on the right. (Fig. 2.) Under local anaesthesia on June 22nd the right basilic vein was exposed at its junction with the cubital vein. A thrombus 8 mm. by 4 mm., occluding the basilic vein to its junction with the cubital vein, was resected between ligatures. The patient continued to have left pleuritic pain for six weeks following the ligation but hemoptysis did not recur. From June 13th, the day of the appearance of the first pleuritic pain, until June 22nd, the date of the ligation of the right basilic vein, the patient's temperature ranged between 98.6° and 102°F. The pulse rate was between 90 and 110 per minute prior to ligation of the vein. Following ligation of the vein both the temperature and the pulse returned to normal in a striking manner. On October 27th chest x-ray showed thickening of the left costophrenic angle with almost complete resolution of the pulmonary infarction of the left lung.

CASE III. M. H., a forty-three year old white female, was admitted to Grady Memorial Hospital on November 1, 1950, with the chief complaint of painful swelling of the left arm and pain in the right side of the chest. Since childhood the patient had had idiopathic epilepsy controlled satisfactorily by anticonvulsant drugs. There was no past history of heart, liver or kidney disease. Ten days before admission the patient had a syncopal episode during which the blood pressure was 90/60 mm. An attempt to give an aqueous solution of ephedrine intravenously resulted in extravasation of the material into the tissue of the left antecubital fossa. Immediately following this an injection of ephedrine in oil was given in the left deltoid muscle, with return of the blood pressure to its normal level of 130/70 mm.

One day prior to admission the patient noted

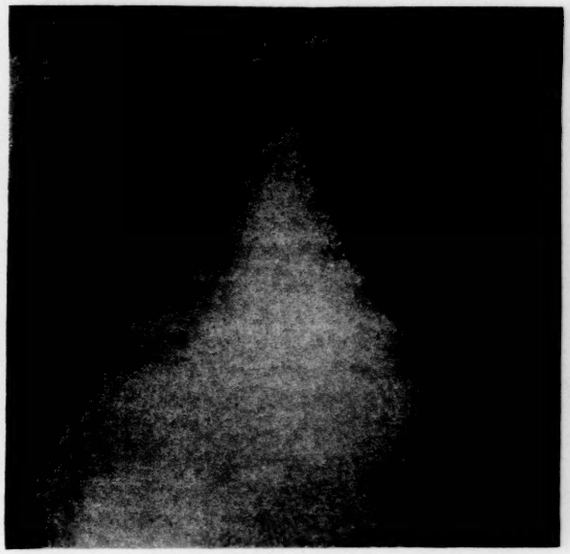


FIG. 2. Chest x-ray of Case II.

edema of the feet and ankles and edema, inflammation and pain in the entire left upper extremity. She suddenly became very dyspneic and had pleuritic pain in the right side of the chest. There was no hemoptysis.

On admission to the hospital the patient was very apprehensive. Her temperature was 100.6°F. Pulse rate was 108 per minute; respirations were 22 to 28 per minute and were shallow; blood pressure was 115/64 mm. There was a large hematoma in the left antecubital fossa. The entire left arm was edematous, tender and was warmer than the right. The left arm was 5 cm. larger than the right. A firm, tender thrombus was palpable in the left subclavian vein. There was impaired resonance in the right base, with bronchial breath sounds, increased vocal fremitus and medium moist rales. The heart was normal to examination. The liver was palpable 3 finger-breadths below the costal margin. There was minimal pedal edema.

Blood Kahn was negative. Urinalysis was normal. Hemoglobin was 11.8 gm. per cent; hematocrit was 34 mm.; sedimentation rate was 100 mm. per hour. White blood cell count was 11,480 per cu. mm., with 80 per cent segmented neutrophils, 2 per cent eosinophils, 2 per cent band cells, 2 per cent stab cells and 14 per cent lymphocytes. Right pleural fluid on November 25th was cultured and Staphylococcus aureus, coagulase positive, and Streptococcus fecalis were obtained. All other cultures, including those for tubercle bacilli, were negative.

Chest x-ray on November 1st revealed a seg-

FIG. 3. Chest x-ray of Case III.

mental area of infiltration or consolidation in the lateral aspect of the right lung base, with possibly a small amount of pleural effusion bilaterally. (Fig. 3.) The findings were compatible with pulmonary infarction. The following day x-ray revealed a rounded density in the posterior portion of the right lung field, resembling a pulmonary infarction. On November 18th the right costophrenic angle was again obscured by pleural fluid and a nodular density obscured the left apex. This was interpreted as an inflammatory process, probably inactive pulmonary tuberculosis. On March 20th some clearing of the process in the right base had occurred. The haziness in the left apex persisted.

On admission anticoagulant therapy with dicumarol was begun. Her prothrombin time was maintained between 20 and 30 per cent of normal from November 2nd to December 14th. Dilantin and phenobarbital were continued. The patient received 100,000 units of penicillin intramuscularly every four hours from November 1st until December 14th. On November 3rd it was thought that acute cor pulmonale was present. The patient was maintained on digitalis and sodium restriction until November 15th, after which time these measures were discontinued.

The patient's temperature ranged between 100° and 102°F. for two days and then remained between 99° and 100°F. for two weeks. However, she again had temperature of 102°F., and chloramphenicol was administered, 0.5 gm. every six hours, because of the probability of secondary bacterial invasion of the pulmonary infarction. The temperature gradually returned to normal. The pulse remained between 100 and 110 per minute throughout hospitalization.

On December 13th the patient suddenly was unable to swallow or talk and it was thought that she had a cerebral embolus. These symptoms remained for several hours. The edema of the left arm subsided entirely. She continued to have right pleuritic pain for three weeks after admission. On dismissal from the hospital on January 3, 1951, a thrombus in the left external jugular vein was palpable.

CASE IV. W. F. R., a twenty-four year old colored male, was admitted to Lawson Veterans Administration Hospital on December 27, 1950, with the chief complaint of left pleuritic pain. He had noted small amounts of rust-colored sputum in the morning for two weeks before admission. On the morning of admission he had fever and pleuritic pain had developed in the base of the left lung.

Examination on admission revealed his temperature to be 99.4°F., blood pressure 134/94, pulse 90 per minute and respirations 24. There was pain on palpation of the left side of the chest from the level of the fifth rib downward. Breath sounds were distant over this area. No rales or friction rub was heard.

White blood cell count was 12,600 per cu. mm., with 1 per cent band cells, 80 per cent segmented neutrophils and 19 per cent lymphocytes. Urinalysis was normal. Hemoglobin was 15.1 gm. per cent. Hematocrit was 49 mm. Sedimentation rate was 23 mm. per hour. Kahn test was negative. Culture of the sputum revealed a normal flora. Stains were negative for acid-fast bacilli.

X-ray of the chest on admission showed elevation of the left diaphragm with some haziness overlying it, indicating pleural irritation and possibly minimal pleural effusion. The lung fields were clear otherwise and the heart was normal. The electrocardiogram was normal.

On the following day the pain was localized in the epigastrium. X-ray of the abdomen was normal. Later the same day the patient expectorated bright red blood and the pleuritic pain became worse. X-ray of the chest revealed an increase in the pleural changes bilaterally, and the diagnosis of pulmonary embolism was made. The hemoptysis continued and the next day the patient was started on depo-heparin and dicumarol. Although the prothrombin time was maintained between 20 and 30 per cent of

normal, the hemoptysis continued for one week after discharge from the hospital. (Fig. 4.)

It was not until eight days after admission to the hospital that the patient experienced pain in the region of the left antecubital vein, which was found to contain a thrombus. This vein had been used several times for venipuncture. No other areas of thrombophlebitis appeared. On the day the thrombus was evident an x-ray of the chest showed changes of bilateral pulmonary emboli with left pleural effusion. X-ray of the chest on January 19, 1951, showed the right lung to be clear, but a density remained in the left base with elevation of the left diaphragm and possibly pleural effusion.

The patient's temperature fluctuated between 98.6° and 100°F. for the first ten days of hospitalization. It gradually fell, reaching normal by the fourteenth day. The pulse rate ranged between 90 and 120 per minute for the first week, after which it was normal.

After the patient's discharge from the hospital on January 24th he continued to have hemoptysis for one week and experienced some aching in the left arm after exercise. During the middle of April he noticed tenderness in the left calf muscles, remaining for one week. On May 1st after driving a long distance by automobile he had some aching in the right arm and shoulder. He was admitted to the hospital on May 9th because of the appearance on that day of pleuritic pain in the base of the right lung and hemoptysis.

The patient's temperature on admission was 102°F. Dulness, rales and pleural friction rub were present in the base of the right lung. There was no evidence of phlebothrombosis or thrombophlebitis in any of the extremities.

Chest x-ray revealed an area of consolidation in the posterior basilar segment of the right lower lobe. A linear scar remained in the left lower lobe as a residual of the previous pulmonary infarction.

The patient's temperature rose to 102°F. each afternoon for one week, after which time it gradually returned to normal. He was given heparin on the night of admission and the prothrombin time was depressed to therapeutic levels with dicumarol therapy between May 9th and May 22nd. At this time he is asymptomatic.

Case v. N. C. P., a forty-two year old colored female, was admitted to Grady Memorial Hospital on January 18, 1951. The patient was in good health until two weeks

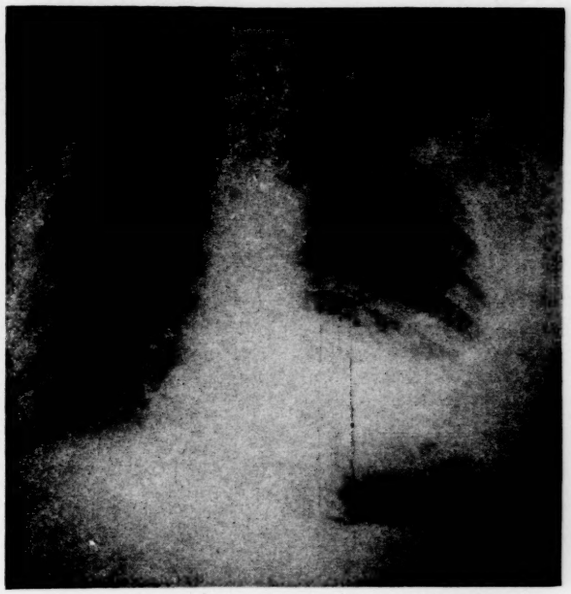


Fig. 4. Chest x-ray of Case iv.

before admission, at which time dyspnea, anorexia, nausea and tenderness developed in the right supraclavicular fossa. Five days prior to admission she had fever, chills and pain in the left side of the chest, for which she received penicillin.

Physical examination on admission revealed her temperature to be 98.2°F., pulse 104 per minute, blood pressure 110/90 and respirations 24 per minute. The patient was not acutely ill. There was a tender, non-pulsatile, non-inflammatory mass 4 cm. in diameter above the right sternoclavicular joint. The neck veins were distended, especially on the right side. Resonance was impaired in both lung bases, with fine moist rales, more marked on the right. The apex impulse was diffuse. The left border of cardiac dulness was 10 cm. to the left of the mid-sternal line. No murmurs were heard. A diastolic gallop rhythm was present. The liver was palpable 4 fingerbreadths below the right costal margin. There was 1 plus edema of the ankles. The venous pressure in the left arm was 160 mm.; in the right arm, 240 mm. The circulation time, left arm-to-tongue, was 47 seconds; right arm-to-tongue, 58 seconds.

Blood Kahn was negative. Urinalysis was normal. Sedimentation rate was 8 mm. per hour. The white blood cell count was 9,150 per cu. mm., with a normal differential count. X-ray of the chest on January 18th demonstrated marked cardiac enlargement, with a moderate pleural effusion on the right and a small pleural

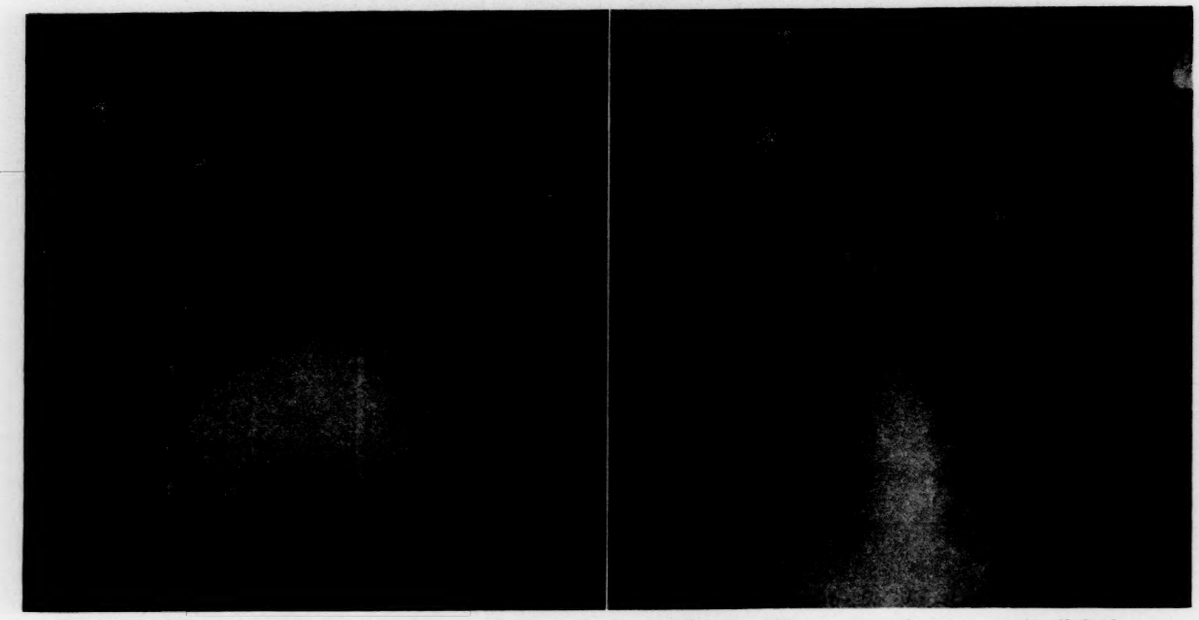


FIG. 5A. Chest x-ray, Case V, on January 18th.

FIG. 5B. Chest x-ray, Case V, on April 2nd.

effusion on the left. (Fig. 5A.) The electrocardiogram on January 19th showed the changes of left ventricular hypertrophy and left ventricular ischemia with digitalis effect.

The patient was digitalized on admission and this medication was continued until March 2nd. She was given a 200 mg. sodium diet. The daily prothrombin time was maintained between 20 and 30 per cent of normal value by daily administration of dicumarol between January 18th and February 2nd. The temperature ranged between 98.0° and 99°F. throughout her hospitalization. The pulse rate varied between 90 and 100 per minute for one week and then gradually returned to normal. On the day following admission the right arm, right side of the neck and the right upper eyelid were edematous. There was no difference in the pulse or temperature of the arms. The edema gradually became less and by February 1st it had disappeared. Slight pain was present on extension of the neck. On January 24th a tender thrombus was palpable in the right supraclavicular fossa, extending 4 cm. cephalad. The symptoms and signs of cardiac failure improved and the patient was discharged from the hospital on February 4th.

On March 2nd there was no evidence of heart failure. Salt restriction was maintained but digitalis was discontinued. The patient was last seen on April 2nd, at which time examination was normal. The thrombosed veins could no longer be palpated. The electrocardiogram showed changes indicative of diffuse epicardial ischemia. X-ray of the chest was normal except for slight increase in the bronchovesicular markings of both bases. (Fig. 5B.)

The initial impression in this case was that the patient had Fiedler's myocarditis and possibly pulmonary emboli were arising from mural thrombi. However, with the findings of thrombophlebitis in the upper extremity, a history of fever, chills and pleuritic pain five days prior to admission to the hospital, and lastly the disappearance of all evidence of heart disease clinically, we believe that the cardiac failure present on admission to the hospital was due to pulmonary emboli originating from thrombophlebitis involving the right subclavian vein and the veins of the right upper extremity.

COMMENTS

In 1940 Veal reviewed the literature of the preceding fifty years and was able to collect only 150 cases of thrombosis of the subclavian and axillary veins. He reported seventeen additional cases.[2] Although thrombophlebitis of the upper extremity is a relatively uncommon condition, it probably occurs more frequently than is generally realized. Over a twelve-year period at the University of Michigan Hospital, chemical thrombophlebitis of the upper extremities resulting from intravenous fluids and medications was included in the discharge diagnoses of

only five cases.[3] However, one week's careful observation on the surgical wards revealed more than this number of cases of thrombophlebitis of the arm. In a series of 1,260 postoperative cases of venous thrombosis occurring in 1,401 different segments of the venous system and complicated by pulmonary embolism only twenty-four or 1.7 per cent involved the upper extremities whereas the lower extremities were involved in 85.6 per cent of the cases.[4] The low incidence of thrombophlebitis reported to occur in the upper extremities has been explained by the rapid emptying of the venous system by frequent movements of the arms and by the short distance through which the blood must flow. It would seem that the statistics concerning thrombophlebitis in the upper extremities are especially subject to criticism since the veins in the arms are rarely examined at autopsy. Because complete autopsies are not permitted or because the thrombus has migrated in its entirety, it frequently is very difficult to determine the source of the primary embolus. In one series of cases it was impossible to determine the site of the thrombus from which the pulmonary embolus originated in over 50 per cent of the cases.[5] Furthermore, it is logical to assume that thrombophlebitis could occasionally occur without signs or symptoms in the upper extremities, as it does in the lower extremities, causing its true incidence to be difficult to ascertain. However, it would seem that the condition is less commonly overlooked in the upper extremities than in the lower since the veins of the arm are superficial and the physical signs are more readily recognized.

Thrombophlebitis of the upper extremities, which may occur under a variety of conditions, is seen in infectious and debilitating diseases, in postoperative patients, following intravenous fluids and medications, complicating polycythemia vera,[6] leukemia and pernicious anemia, and secondary to infections involving regions adjacent to or drained by the veins. The clinical entity, thrombophlebitis of effort or trauma, occurring predominately in males and in the right arm has been described.[7] Veal and Hussey state that in their experience neoplasm is the most common cause of thrombophlebitis of the axillary and subclavian veins and that carcinoma of the breast is the most common malignancy present.[8] Four of the seven cases of thrombophlebitis of the upper extremity reported by Sproul occurred in patients with malignancy.[9] In 1900 Welch collected twenty-eight cases of thrombophlebitis involving the veins of the neck, arm and chest associated with heart disease, chiefly mitral stenosis with or without mitral insufficiency, and with congestive failure.[10] Twenty-two of the twenty-eight cases involved the left arm; this extremity was involved alone in fifteen cases. This is in sharp contrast to the predominant involvement of the right arm in thrombosis due to trauma or effort. In 1943 Veal and Hussey reported sixteen cases of congestive failure complicated by thrombophlebitis of the upper extremity.[8] In thirteen of these cases slowing of the circulation was the only causative factor. In these patients severity of the heart failure, not the type of heart disease, was considered the important factor in the production of the thrombophlebitis. Thirty to forty per cent of patients with thromboangitis obliterans have migrating phlebitis which can involve the upper extremities. Thrombophlebitis in the upper extremities may occur in a retrograde manner from inflammatory processes within the thorax. It is also seen following radical mastectomy with obstruction and destruction of venous trunks. Of the sixteen cases comprising the series herein presented the etiology of the thrombophlebitis was unknown in six cases, due to chemical irritation in five, traumatic in two, associated with leukemia and Buerger's disease in one case each and secondary to local infection in one case.

The history and physical examination are usually sufficient to make the diagnosis of thrombosis of the veins of the arm. Pain in the extremity is usually present early in the course of the illness, and edema and weakness of the extremity occur. It is believed by Ochsner and Debakey that one of the most important factors in the production of pain and edema in thrombophlebitis is vasospasm, resulting from vasoconstrictor impulses originating in the involved venous segment and coursing through the sympathetic ganglia to reach the terminal arterioles.[11] This vasospasm may be severe enough to produce gangrene of the fingers. The thrombus in the involved vein is often palpable. The systolic pressure in the affected arm is normal or slightly elevated. The venous pressure is usually elevated but this may occur only after exercise of the arm.

To be considered in the differential diagnosis is arteriovenous fistula involving the axillary and brachial vessels, which will result in en-

largement of the arm and superficial vessels. In this condition, however, the veins pulsate, a bruit and thrill are present and the involved arm is warmer than the opposite member. The oxygen content of the venous blood is elevated whereas it is lowered in thrombosis. Obstruction of the mediastinal veins will result in elevation of the venous pressure in both arms. With edema of the arm not due to venous obstruction the venous pressure is normal after exercise as well as at rest. Venography has been utilized to demonstrate accurately the location of the thrombus, but this method of diagnosis has gradually been discarded.

The thrombus may be absorbed; it may become organized and permanently obstruct the vessel; or it may be recanalized, as was demonstrated roentgenographically by Perlow and Barth.[12] Progression of the thrombus may occur, with involvement of the entire venous system of the extremity with extension into the dural sinuses and intracerebral veins.[13] The disability

TABLE I

PULMONARY EMBOLISM AND INFARCTION WITH REFERENCE TO LOCATION OF THROMBUS

Author	Description of Cases	Location of Venous Segments Involved	
Henderson[15]	313 cases of pulmonary embolism	Pelvis and lower extremity	207
		Heart	13
		Neck and chest	4
		Axillary	3
Belt[16]	56 cases of pulmonary embolism		
	(1) 25 cases of congestive heart failure with pulmonary emboli	Lower extremity	8
		Heart	5
		Lower extremity and heart	4
		Not determined	4
		Prostatic veins	2
		Brachial vein	1
		Jugular vein	1
	(2) 31 cases of pulmonary emboli in debilitated patients and convalescents	Pelvis and lower extremity	25
		Not determined	6
Sagall, Bornstein and Wolff[19]	108 cases of pulmonary embolism	Lower extremity	
		Definite	60
		Presumptive	30
		Heart	
		Definite	3
		Suggestive	6
		Pelvis	
		Definite	5
		Suggestive	2
		Veins of arm	2
Neuhof and Klein[5]	88 cases of pulmonary embolism	Undetermined	45
		Pelvis and lower extremity	32
		Heart	3
		Right antecubital	1
Cohn and Walsh[20]	96 proven cases of fatal pulmonary emboli	Pelvis and lower extremity	55
		Undetermined	37
		Heart	7
		Neck	3
		Brachial	1
Moran[21]	147 cases of pulmonary emboli found in 635 consecutive autopsies	Pelvis and lower extremity	44
		Prostate	44
		Not determined	32
		Heart	17
		Prostate and other sources	8
		Left arm	1
		Sagittal sinus	1
Dehlinger and Riemenschneider[22]	74 cases of pulmonary embolism	Pelvis and lower extremity	36
		Not determined	25
		Lower extremity (questionably)	6
		Heart	3
		Heart and inferior vena cava tributaries	3
		Arm (clinically)	1

following the acute state varies according to the extent of involvement of the deeper venous system and the degree of collateral circulation. There may be no symptoms while the extremity is at rest, but with exercise, weakness, pain, fatigue and edema may occur. The term "post-

arm and elevation of the extremity are usually sufficient. Because of the tendency for pulmonary embolism to occur in cases associated with congestive failure, Veal and Hussey have recommended ligation of the subclavian vein proximal to the thrombus.[8] Sympathetic block with novo-

TABLE II

Author	Description of Cases	Location of Venous Segments Involved		Complication
Welch[10]	28 cases of thrombophlebitis of arm in patients with cardiac disease	Neck Axillary Brachial Left lateral sinus of brain	60 11 6 1	No massive emboli reported; undetermined whether pulmonary infarctions were due to emboli derived from venous thrombi
Discussion of Welch's paper	6 similar cases	Arm Not stated Neck Lower extremity	3 3 2 1	No mention of pulmonary emboli
Schepleman[14]	1 case of thrombophlebitis of arm possibly due to trauma	Left axillary, brachial and subclavian		Pulmonary embolism occurred
Moure (quoted in[7])	1 case of thrombophlebitis of arm following fracture of humerus	Subclavian		Fatal pulmonary embolism occurred
Barker[17]	79 cases of idiopathic or primary thrombophlebitis			
	(1) 40 cases of recurrent idiopathic thrombophlebitis	Lower extremity Superficial veins of arm Superficial veins of abdomen Superficial veins of scrotum Median basilic	83 4 3 1 1	12 cases of pulmonary infarction, all from leg veins; (unable to exclude with certainty localized pulmonary thrombophlebitis)
	(2) 39 cases of single episode of thrombophlebitis	Lower extremity External jugular	38 1	3 cases of pulmonary embolism, all from leg veins
Veal and Hussey[8]	46 cases of subclavian and axillary vein thrombosis			
	(1) 16 cases associated with congestive failure			(1) 9 pulmonary emboli, fatal in 7 cases
	(2) 10 cases due to trauma or effort			(2) Authors state that pulmonary emboli practically never occur
	(3) 18 cases secondary to neoplasm			Authors state that pulmonary emboli do not occur to their knowledge
	(4) 2 cases secondary to postoperative scarring			
Roelsen[18]	7 cases of primary thrombosis of axillary vein (traumatic)			Pulmonary infarction occurred in 1 case
Vander Veer, Kuo and Marshall[23]	222 cases of venous thrombosis			89 cases of pulmonary emboli, 23 of which were fatal; one fatal embolus originated from internal jugular, subclavian and innominate veins

thrombotic syndrome" has been applied to this symptom complex which may persist for several years, subsiding as the collateral circulation becomes adequate.

Anticoagulant therapy, limited motion of the

cain, as advocated by Ochsner and Debakey, has resulted in decrease in the edema, pain and inflammation.[11] The rapid disappearance of edema sometimes seen following ligation and resection of the thrombosed venous segment

would seem to indicate that the response is due to the interruption of sympathetic impulses originating in the segment.

In Table I we have summarized various series of cases of pulmonary embolism and infarction with reference to the location of the thrombus. In Table II we have presented series of cases of thrombophlebitis, in some of which the upper extremity served as a source for pulmonary embolism.

Although the cases cited heretofore do not represent a complete review of the literature, we believe that the complication of pulmonary embolism originating from thrombophlebitis of the upper extremity has not been adequately emphasized in the past. The condition undoubtedly occurs much more frequently than is generally appreciated and is often misdiagnosed as pneumonia, myocardial infarction, congestive failure or atelectasis. Hussey has reported forty-three cases of septic pulmonary emboli, in fourteen of which the source was the arm veins.[24] The majority of these cases occurred in heroin addicts, accounting for the high percentage of upper extremity involvement. The author states that septic pulmonary embolism differs sharply in pathology, clinical manifestations and laboratory findings from the more common non-infected pulmonary embolism. The problem of recognition of pulmonary embolism when it is present remains an important one.

SUMMARY

Five cases of thrombophlebitis of the upper extremity in which pulmonary embolism occurred as a complication are presented. The etiology was secondary to chemical irritation in two cases, was unknown in one case and was probably traumatic in the fifth case. All of the patients having pulmonary emboli received anticoagulant therapy. Pulmonary emboli were controlled satisfactorily in two of the five patients. One patient died from repeated pulmonary emboli originating in the right axillary, brachial and subclavian veins, and multiple pulmonary infarctions were demonstrated at postmortem examination. Venous ligation was necessary in one of the remaining cases, and the fifth patient continued to have hemoptysis for six weeks even though the prothrombin time was maintained at therapeutic levels. This patient subsequently had recurrent thrombophlebitis of the upper extremity with pulmonary embolism, from which he recovered with conservative therapy.

Addendum. Since the preparation of this paper we have observed another patient with pulmonary infarction secondary to thrombophlebitis of the upper extremities resulting from intravenous clyses administered in another hospital. He also had syphilitic cardiovascular disease with aortic insufficiency and marked angina pectoris. Anticoagulant therapy was instituted on admission to Emory University Hospital, but the patient died thirty-six hours after admission while asleep. Whether death resulted from pulmonary infarction or myocardial infarction cannot be stated. Permission for necropsy was not granted.

REFERENCES

1. Allen, A. W. Thrombosis and embolism. *Bull. New York Acad. Med.*, 22: 169, 1946.
2. Veal, J. R. Thrombosis of the axillary and subclavian veins. *Am. J. M. Sc.*, 200: 27, 1940.
3. Buxton, R. W. Venous thrombosis in the upper extremity. *Univ. Hosp. Bull., Ann Arbor*, 12: 53, 1946.
4. Barker, N. W., Nygaard, K. K., Waters, W. and Priestly, J. T. A statistical study of postoperative venous thrombosis and pulmonary embolism. Location of thrombosis: relation of thrombosis and embolism. *Proc. Staff Meet., Mayo Clin.*, 16: 33, 1941.
5. Neuhof, H. and Klein, S. H. Massive pulmonary embolism: based in part on study of 88 fatal cases. *J. Mt. Sinai Hosp.*, 11: 87, 1944–1945.
6. Stover, L. and Herrell, W. E. Extensive thrombosis of the right subclavian and axillary veins associated with thrombophlebitis, lymphedema, and polycythemia vera. *Proc. Staff Meet., Mayo Clin.*, 15: 817, 1940.
7. Matas, R. Primary thrombosis of the axillary vein caused by strain. *Am. J. Surg.*, 24: 642, 1934.
8. Veal, J. R. and Hussey, H. H. Thrombosis of the subclavian and axillary veins. Report of 46 cases. *Am. Heart J.*, 25: 355, 1943.
9. Sproul, E. E. Carcinoma and venous thrombosis: the frequency of association of carcinoma in the body or tail of the pancreas with multiple venous thrombosis. *Am. J. Cancer*, 34: 566, 1938.
10. Welch, W. H. Venous thrombosis in cardiac disease. *Tr. A. Am. Physicians*, 15: 441, 1900.
11. Ochsner, A. and Debakey, M. Therapeutic considerations of thrombophlebitis and phlebothrombosis. *New England J. Medicine*, 225: 207, 1941.
12. Perlow, S. and Barth, E. E. Primary thrombosis of the axillary and brachial veins. Report of two cases. *Quart. Bull. Northwestern Univ. M. School*, 16: 123, 1942.
13. Esselborn, V. and Janchar, L. J. Propagating axillary and subclavian venous thrombosis with extension into the dural sinuses and intracerebral veins. *Ohio State M. J.*, 42: 739, 1946.

14. Schepelmann. Demonstration eines Patienten mit Thrombose der linken Vena subclavia seltener Aetiologie. *München. med. Wchnschr.*, 46: 2444, 1910.
15. Henderson, E. F. Fatal pulmonary embolism. *Arch. Surg.*, 15: 231, 1927.
16. Belt, T. H. Thrombi and pulmonary embolism. *Am. J. Path.*, 10: 129, 1934.
17. Barker, N. W. Primary idiopathic thrombophlebitis. *Arch. Int. Med.*, 58: 147, 1936.
18. Roelsen, E. Primary thrombosis of the axillary vein. *Acta chir. Scandinav.*, 90: 547, 1944–1945.
19. Sagall, E. L., Bornstein, J. and Wolff, L. Clinical syndrome in patients with pulmonary embolism. *Arch. Int. Med.*, 76: 234, 1945.
20. Cohn, R. and Walsh, J. The incidence and anatomical site of origin of pulmonary emboli. *Stanford M. Bull.*, 4: 97, 1946.
21. Moran, T. J. Pulmonary embolism in nonsurgical patients with prostatic thrombosis. *Am. J. Clin. Path.*, 17: 205, 1947.
22. Dehlinger, K. and Riemenschneider, P. Pulmonary embolism: analysis of 74 autopsy cases since 1941. *New England J. Med.*, 240: 497, 1949.
23. Vander Veer, J. B., Kuo, P. T. and Marshall, D. S. II. Experiences with venous thrombosis and pulmonary embolism, with special reference to anticoagulant therapy. *Am. J. M. Sc.*, 219: 117, 1950.
24. Hussey, H. H. The pathogenesis of septic pulmonary embolism. *M. Clin. North America*, 34: 1751, 1950.

Some Supravital Observations on the "L.E." Phenomenon*

ROBERT J. ROHN, M.D. *and* WILLIAM H. BOND, M.D.
Indianapolis, Indiana

In 1948 Hargraves, Richmond and Morton[1] described a peculiar inclusion body which was found in the polymorphonuclear neutrophils of the bone marrow of patients with acute disseminated lupus erythematosus. They postulated that this was a lytic-phagocytic phenomenon in which the inclusion body was either a degenerated phagocytized lobe of the affected polymorphonuclear neutrophil, or the autolyzed phagocytized nucleus of another polymorphonuclear neutrophil. The authors did not, at this time, observe these peculiar cells in the peripheral blood. They called the phagocytic neutrophil with its inclusion body the "L.E." cell and suggested that it might prove to be highly specific for acute disseminated lupus erythematosus.

The observations made by Hargraves et al.[1] were quickly confirmed by Haserick and Sundberg,[2] who found these "L.E." cells present in the bone marrow of four of five cases of acute disseminated lupus erythematosus which they observed. They suggested that the phagocytized inclusion body was the nuclear material of the lymphocyte. They failed to find these "L.E." cells in their cases of subacute and chronic lupus erythematosus.

Since these first reports numerous investigators have found "L.E." cells in the bone marrow and the peripheral blood of patients with acute disseminated lupus erythematosus. In many laboratories throughout the country the attempt to find "L.E." cells is an integral part of the diagnostic work-up on any patient suspected of acute disseminated lupus erythematosus.

The "L.E." phenomenon has been found in a high percentage of patients with acute disseminated lupus erythematosus and only a small number of false positives has been reported. Thus Montgomery and MacCreight[3] reported the finding of "L.E." cells in a case of multiple myeloma by Hargraves (personal communication). Berman et al.[4] reported finding "L.E." cells in a case of pernicious anemia and one of dermatitis herpetiformis. Kurnick[5] noted "L.E." cells in a patient with miliary tuberculosis. Lee, Michael and Vural found "L.E." cells in a case of hemolytic anemia and reported finding a pseudo-"L.E." cell in the bone marrow of a patient with amyloidosis. In the latter case the inclusion body was proved to be amyloid. From a consideration of their own cases and the collected literature Lee et al.[6] concluded that the finding of "L.E." cells is, with few exceptions, highly specific for acute disseminated lupus erythematosus.

There is unanimity of opinion as to the general mechanism of formation of the "L.E." cell. Two constituents seem to be needed for the demonstration of this phenomenon. The first constituent is the "L.E." factor. This factor[7] is thought to be an abnormal portion of the plasma gamma globulin fraction present in the plasma of a high percentage of patients with acute disseminated lupus erythematosus. This portion of the plasma globulin fraction has not been demonstrated in normal human plasma and rarely, if at all, in the plasma of patients with diseases other than acute disseminated lupus erythematosus. Haserick and Lewis[8] isolated this factor by electrophoresis and dialysis. This isolated factor seemed to have antigenic properties, for when it was injected into rabbits antibodies were formed which were effective in blocking the formation of "L.E." cells when added to a suspension of leukocytes in the plasma from patients with acute disseminated lupus erythematosus. This "L.E." factor seems to be instrumental in the rapid autolysis of leukocytes which occurs in this disease.

* From the Department of Experimental Medicine, Division of Hematology, Indiana University Medical Center. Presented before the Twenty-fourth Annual Meeting of the Central Society for Clinical Research, Chicago, November 2nd, 1951.

The second constituent is a phagocytic leukocyte which ingests the autolyzed cell. That the inclusion body is nuclear material was first demonstrated by Hargraves et al.[1] employing Feulgen stain. This has since been repeatedly confirmed.

The complete "L.E." phenomenon is then a two-phase process. In the first phase there is rapid, nuclear, leukocytic autolysis, and in the second phase the autolyzed leukocytic nuclear material is phagocytized by other intact leukocytes.

There has been some divergence of opinion as to what constitutes the precursor of the "L.E." cell inclusion body. Similarly, opinion has varied as to what type of leukocyte displays phagocytic activity in the formation of the "L.E." cell.

As to the constitution of the "L.E." inclusion body the following theories have been offered. Hargraves et al.[1] suggested that this inclusion body was an autolyzed lobe, or the total nucleus of a mature polymorphonuclear neutrophil. Haserick and Sundberg[2] at first suggested that this inclusion body was a lymphocyte. Later, Haserick, Lewis and Bortz[7] suggested that the inclusion substance was of megakaryocytic or platelet origin. In a study of this problem Moyer and Fisher[9] suspended normal mature neutrophilic leukocytes in old bank blood. They similarly suspended normal mature neutrophilic leukocytes in a suspension of leukemic lymphocytes. To both suspensions they added plasma from a patient with acute disseminated lupus erythematosus. They noted a much greater yield of "L.E." cells in the suspension containing the leukemic lymphocytes, and observed many of these inclusion bodies to have clearly defined lymphocytic characteristics. From this experiment they concluded that the "L.E." cell inclusion body was principally of lymphocytic origin. Lee et al.[10] at first stated that the "L.E." cell inclusion body was the autolyzed nucleus of a mature neutrophilic leukocyte. Later Lee et al.[6] reported that the "L.E." inclusion body was lymphocytic and nuclear neutrophilic leukocytic in origin.

Hargraves et al.[1] stated that the phagocytic component of the "L.E." cell was practically always a mature neutrophilic polymorphonuclear leukocyte. Moyer and Fisher[9] found the "L.E." inclusion body in metamyelocytes, band form polymorphonuclear neutrophils, mature polymorphonuclear neutrophils, polymorphonuclear eosinophils and monocytes. Lee et al.[6] found "L.E." inclusion bodies in mature polymorphonuclear neutrophils and, in one case, in monocytes.

There are many methods utilized for demonstrating the "L.E." phenomenon. In all the methods reported the critical factor is the time elapsed between obtaining the specimen (or adding the "L.E." factor to normal leukocytes) and preparation of the specimen. Thus up to forty minutes are needed for maximal autolysis with resultant phagocytosis to occur. Of lesser significance is the density of cells, a direct proportion existing between the concentration of leukocytes and the ease with which "L.E." cells are found. Hargraves,[11] by using various anticoagulants, demonstrated that the "L.E." phenomenon was not dependent upon any specific anticoagulant. Various authors used clotted blood,[12] defibrinated blood and blood collected in silicone-coated containers[13] and demonstrated that the "L.E." phenomenon can occur in the absence of any anticoagulant.

Both bone marrow[12,13] and peripheral blood specimens[11,14] have been utilized to demonstrate the "L.E." phenomenon. Some authors have suspended normal bone marrow[15] or peripheral blood buffy coats[16] with plasma obtained from a patient with acute disseminated lupus erythematosus to demonstrate the "L.E." phenomenon.

All authors agree that there is no satisfactory direct method for demonstrating the "L.E." cell.

There have been only two authors who have at the date of this writing mentioned observations on the unfixed "L.E." cell with supravital staining. Hargraves et al.[1] make brief mention of the supravitally stained "L.E." cell, but fail to elaborate on either the description of the cell or the technics employed in this examination. Moyer and Fisher,[9] in studying the phagocytosis of leukemic lymphocytes injected into a suspension of normal polymorphonuclear neutrophils in plasma from patients with acute disseminated lupus, employed Janus green to study the phenomenon. These authors also failed to give the exact technics employed. Janus green effectively stains mitochondrial structures. Failure of Janus green to stain the granules and vacuoles, however, lessens its critical differential value when used alone.

TECHNICS EMPLOYED

At the hematologic research laboratory of Indiana University Medical Center we have

adopted the supravital staining technics employed by Wiseman and Doan in the research medical department of Ohio State University Medical Center. We use this technic for all routine examinations of peripheral blood and bone marrow referred to our service. We use fixed stain preparations only for permanent records. During the year 1950–1951 we have observed "L.E." cells in the peripheral blood and/or bone marrow of five patients, whose case reports are briefly summarized in this paper. While our series of cases is small, the paucity of supravital studies on the "L.E." phenomenon makes such a report of some interest. Moreover, we have what we regard as a direct method for demonstrating the "L.E." cells without subjecting the blood to anticoagulant substances, centrifugation or other special manipulative procedures.

Because of the infrequency with which supravital staining is employed, it might be pertinent at this point to elaborate on our procedure in obtaining, preparing and staining peripheral blood and bone marrow specimens.

The staining method utilized was first described by Sabin.[17] In this method separate saturated solutions of neutral red and Janus green in neutral anhydrous ethyl alcohol are prepared and maintained as stock solutions. The two dye solutions are mixed just before preparing a fresh supply of stained slides. In the mixing of these dyes the stock solutions are added in a ratio of approximately five parts of neutral red to one part of Janus green to 5 cc. of neutral anhydrous ethyl alcohol. It has been found that approximately 33 drops of neutral red and six drops of Janus green will yield maximal staining effect with minimal deleterious effect upon the cellular elements. It should be emphasized that differing stock solutions will, within a rather narrow limit, necessitate increasing or decreasing the amount of dye or its component parts. The stock solutions are stable for long periods of time and a relatively small amount will stain a large number of slides.

The stain mixture is flooded evenly over one side of a scrupulously clean, flamed slide. The wet, stained slide is then passed quickly over a Bunsen burner flame achieving rapid evaporation and avoiding ignition of the alcohol. The dried stain should then appear as an evenly spread film over one side of the slide giving a reddish-pink cast to the slides. Seventy-five to a hundred of these slides can be prepared from a 5 cc. solution of dye mixture, and these slides can then be stored in dry, dust proof slide boxes for future use. Such slides can be used within one to two months after preparation. While this staining procedure may sound complicated and tedious, the actual time in making these preparations will be found to be much less than the aggregate time spent staining an equivalent number of preparations by conventional fixed-staining procedures.

In making peripheral blood differential preparations a scrupulously clean, dry "O" thickness coverslip is touched to a drop of blood obtained by puncturing the finger or ear lobe with a Bard-Parker blade, Hagedorn needle or other appropriate instrument. The coverslip is then dropped, blood side down, on a previously stained slide. The blood should spread evenly under the weight of the coverslip only; no extraneous pressure to facilitate spreading should be employed. The coverslip should then be rimmed with vaseline to prevent drying and crenation of cells. A good preparation will be one cell layer thick. Too thick or too thin a preparation will result in distortion of the cells.

To obtain bone marrow specimens we employ a simple 18-gauge "Barker-Biers" spinal needle, cut down to 2½ inches shaft length, with a rather shallow bevel. Such a needle is easily handled, safe if properly used, and easily replaceable. Any usual marrow site is employed. Marrow is aspirated with a sterile, absolutely dry 20 cc. syringe. One quarter to ½ cc. of marrow is the desired amount of marrow aspirant. The specimen is then extruded upon a clean, dry, unstained slide. Marrow fragments are observed as small white flecks in the blood. These fragments can then be picked up along with 0.025 to 0.05 cu. mm. of diluent blood with a Thoma white blood cell pipette. The fragments and diluent blood are then placed upon a clean, dry "O" thickness coverslip which is gently dropped, marrow side down, upon a previously stained slide. After the specimen has completed spreading under the weight of the coverslip, the latter can be rimmed with vaseline to prevent drying. The resultant preparation should then be a one-cell layer thick lake of diluent blood surrounding a small white island of marrow fragment. Any lack of cleanliness will result in poorly spreading preparations. Any water in syringe, needle or on the slides or cover slips will cause lysis of cells. Similarly,

mechanical pressure on the coverslip will result in cell destruction. The specimens can be studied, if refrigerated, for eight to twelve hours after preparation although maximal staining with minimal cellular death can best be observed within twenty to forty minutes after the slides have been prepared. Pull slip preparations can be obtained for fixed staining and permanent record at the same time supravital preparations are made.

Using this technic we have examined approximately 5,000 peripheral blood and 800 bone marrow specimens of patients referred to the hematology service during the past year. As noted previously, we have demonstrated "L.E." cells in five patients during this period of time. Their case histories are here briefly summarized.

CASE HISTORIES

CASE I. A twenty year old student was in good health until March 30, 1949, at which time she developed edema of the right upper eyelid. Later a nodule became palpable on the lateral margin of the globe of the right eye. A right preauricular node showed only lymphoid hyperplasia on biopsy. In March, 1950, she began having pain and stiffness in various joints. In March, 1951, she became acutely ill with fever of 103°F., severe myalgia and pharyngitis. At this time she had axillary lymphadenopathy, minimal swelling of several joints, palpable liver and spleen. Hemogram at this time revealed hemoglobin of 13 gm., erythrocyte count of 4,070,000, total white count of 4,850 with differential showing 57 per cent polymorphonuclear neutrophils, 1 per cent eosinophils, 2 per cent neutrophilic "C" myelocytes, 20 per cent metamyelocytes, 7 per cent lymphocytes, 7 per cent monocytes, 4 per cent Rieder cells, 2 per cent Türk cells; reticulocytes were 1.0 per cent and platelets 919,820. Bone marrow on March 16, 1951, appeared normally cellular, but contained many polymorphonuclear neutrophils which had the classical appearance of the "L.E." cells described by Hargraves. Subsequent hemograms revealed these "L.E." cells in the peripheral blood. Other laboratory examinations including blood chemistries, urinalyses, blood cultures, agglutinations, biopsy of lymph node, x-rays of chest, ankles, feet and hands and intravenous pyelography were normal. Total serum proteins were 7.3 gm. per cent with albumin of 3.7 gm. per cent and globulin of 3.6 gm. per cent. The patient became asymptomatic on no specific therapy and remained so until June 1, 1951, when she had return of all her previous symptoms, and in addition a butterfly type of rash on her face which was accentuated by exposure to light. Bone marrow on June 1, 1951, showed a marked increase in the number of "L.E." cells. On June 2, 1951, she developed severe dyspnea and tachycardia with hyperpyrexia. She was placed on cortisone therapy and showed dramatic response to this therapy, becoming free of all symptoms within a few days. She was discharged from the hospital on June 20, 1951, and has apparently been in remission to date while receiving maintenance doses of cortisone.

CASE II. A thirteen year old girl was admitted to the Pediatrics Service of the Indiana University Medical Center for the first time on March 31, 1951. Her illness had begun one year prior to admission when she began having migratory pains and occasionally swelling involving several joints, low grade evening fever, transitory skin rashes and occasional stabbing pains in the chest. The past history revealed that eleven years previously she had had some sort of reaction to sulfonamides, but had again been given these drugs one year before admission without any reaction being noted. Physical examination on this admission revealed only mild pallor and slight swelling and tenderness of the right leg. There was no splenomegaly nor skin lesions at this time. Hemogram revealed hemoglobin of 11.4 gm., erythrocyte count of 4,210,000, total white blood count of 1,150 with differential showing 45 per cent polymorphonuclear neutrophils, 45 per cent lymphocytes and 10 per cent eosinophils. Bone marrow on April 10, 1951, was somewhat hypoplastic. The striking feature of the marrow was the presence of large numbers of neutrophilic "L.E." cells and several eosinophilic "L.E." cells. Increased numbers of plasma cells, monocytes and eosinophils were considered indicative of "marrow toxicity." Total serum proteins were 7.1 gm. per cent with albumin of 4.5 gm. per cent and globulin of 2.6 gm. per cent. Numerous blood chemistries, urinalyses, hormone studies, blood cultures, complete skeletal and chest x-rays and electrocardiograms were all within normal limits. Repeat bone marrow on April 16, 1951, showed essentially the same picture as the first marrow examination with large numbers of "L.E." cells present. Her course in the hospital

was uneventful and the patient was discharged asymptomatic on April 21, 1951. She was readmitted to the hospital on May 14, 1951, complaining of weight loss, malaise, fever, migratory joint pains and anorexia. For the first time an erythematous macular rash was noted over malar eminences and the bridge of the nose. Adrenocorticotropic hormone was discontinued on June 29, 1951, at which time she was again having migratory joint pains and low grade fever. Bone marrow on this date again showed evidence of toxicity and 7 per cent "L.E." cells, with most of the polymorphonuclear neutrophils displaying nuclear autolysis.

CASE III. A forty-nine year old mechanic was admitted to the Medical Service of the Indiana University Medical Center on July 14, 1951, complaining of bleeding gums of four days' duration. He had enjoyed good health until November, 1950, when he had an upper respiratory infection which was followed by pain and tenderness in several joints. At this time he was treated by his family doctor with penicillin and sulfonamides to which he was said to have had a reaction characterized by increased muscle and joint pains, vertigo, abdominal distention and pleuritic pains in the left chest. He made an uneventful recovery from this illness and felt well until April, 1951, when there was a return of joint pains which became progressively more severe and did not respond to a course of penicillin therapy. On July 10, 1951, on the advice of his family doctor, he had all of his teeth extracted. Following the extraction there was profuse bleeding from the alveolar sockets and the gingiva. He was hospitalized elsewhere and given a total of nine blood transfusions. Following the first of these he noticed itching and tingling of the skin and shortly thereafter multiple petechiae and purpuric spots. Because of continued bleeding which failed to respond to blood transfusions he was transferred to the Indiana University Medical Center. Physical examination on admission revealed an acutely ill patient who was expectorating bright red blood which could be seen to be oozing from the gingiva and alveolar sockets. Petechiae and purpuric areas were extensively scattered over the entire body including the mucous membranes of the mouth. Temperature was 101°F. rectally. Heart and lungs were normal. Blood pressure was 112/72. The abdomen was not tender and contained no palpable viscera or masses. There was some tenderness and pain elicited on movement of the shoulder joints. Hemogram on admission revealed hemoglobin of 13.0 gm., erythrocyte count of 4,160,000, total white blood count of 3,800 with differential of 74 per cent polymorphonuclear neutrophils, 10 per cent small lymphocytes, 2 per cent intermediate lymphocytes, 8 per cent monocytes, 4 per cent plasma cells and 2 per cent basophils; reticulocytes were 0.5 per cent; no platelets were seen. Bone marrow examination on the day of admission showed evidence of acute toxicity as indicated by cytolysis, large numbers of phagocytic clasmatocytes, large young plasma cells, stimulated monocytes and left shift in the granulocytes to "B" myelocyte level. Megakaryocytes were not seen. Polymorphonuclear neutrophils having the characteristic appearance of "L.E." cells made up 13 per cent of the total marrow white blood count. On July 16, 1951, peripheral blood was found to contain 13 per cent "L.E." cells. Urinalyses, blood chemistries, blood cultures, x-rays of peripheral joints, spine and chest were within normal limits. Total serum proteins were 6.2 gm. per cent with albumin of 3.8 gm. per cent and globulin of 2.4 gm. per cent. An electrocardiogram on July 16, 1951, showed a pattern suggestive of a recent anterior myocardial infarction; by August 7, 1951, the pattern had changed to that of incomplete right bundle branch block. A presumptive diagnosis of acute disseminated lupus erythematosus was made in spite of the patient's age and sex. Because of his critical condition he was placed on adrenocorticotrophic hormone therapy on the day of admission, with initial dosage of 240 mg. per day. On this therapy there was dramatic improvement with return of temperature to normal in twenty-four hours, disappearance of all symptoms within a few days and disappearance of "L.E." cells from the peripheral blood and bone marrow by August 7, 1951. On August 23, 1951, after adrenocorticotrophic hormone had gradually been reduced to 20 mg. a day, the patient had recurrence of fever and arthralgia and bone marrow was found to contain 16 per cent "L.E." cells. After the dosage of adrenocorticotrophic hormone was increased the patient again became asymptomatic and was discharged on a maintenance dose of adrenocorticotrophic hormone.

CASE IV. An eighteen year old student was admitted to the Medical Service of the Indiana University Medical Center on July 22, 1951. At

the age of fourteen years it had been noted that she periodically had a rash with a butterfly distribution on her face. At the age of sixteen years she had an illness characterized by lethargy, malaise, joint pain and swelling, and pleurisy which was diagnosed as "rheumatic fever." Recovery from this illness was never complete, and by the Spring of 1951 she developed anemia and fever which became progressively more marked and was accompanied by intensification of the butterfly rash on her face. On admission to the hospital she was found to be acutely ill with a temperature of 101°F. There was a maculopapular rash covering the face in a butterfly distribution and also present on the neck, forehead and left knee. Her eyelids were edematous. Nasal and oral mucous membranes contained ulcerative lesions. Slight cervical and axillary adenopathy were present. Breath sounds were of bronchovesicular quality and were diminished at both lung bases. Her heart was not remarkable and blood pressure was 110/70. No abdominal viscera or masses were palpable. There was slight swelling of both knee joints. No edema was present. Laboratory findings were as follows: Urinalyses showed low specific gravity (1.006–1,010) and persistent albuminuria, with sediment containing many pus cells and on several occasions moderate numbers of intact erythrocytes. Serology was negative. Urine culture showed Strep. viridans, E. coli, and coagulase-positive Staph. aureus. Total non-protein nitrogen ranged from 135 mg. per cent to 210 mg. per cent. Spinal fluid was normal and blood culture was negative. Serum sodium was 130 mEq./L. Total serum proteins were 6.2 gm. per cent with albumin of 2.3 gm. per cent and globulin of 3.9 gm. per cent. Serum potassium was 4 mEq./L. Sedimentation rate was 30 mm./hr. Hemogram on admission revealed hemoglobin of 8.4 gm., erythrocytes 2,480,000, total white blood count 6,800 with differential showing 41 per cent polymorphonuclear neutrophils, 3 per cent neutrophilic "B" myelocytes, 7 per cent neutrophilic "C" myelocytes, 3 per cent metamyelocytes, 28 per cent small lymphocytes, 1 per cent intermediate lymphocytes, 3 per cent Türk cells, 10 per cent active monocytes, 1 per cent young monocytes, 1 per cent epithelioid monocytes and 1 per cent "L.E." cells. Platelets were 263,350; reticulocytes were 1.7 per cent. Bone marrow on admission showed non-specific toxic changes with left shift in myelocytic and erythroid series. Marrow contained 7.5 per cent "L.E." cells on differential count.

Her course in the hospital was progressively downhill with daily spiking temperatures to 103°F., marked weakness and delirium. There was no clinical response to adrenocorticotrophic hormone which was begun on July 26, 1951; however, repeat bone marrow on August 2, 1951, showed less evidence of toxicity and reduction of number of "L.E." cells to 1.5 per cent. "L.E." cells disappeared from the peripheral blood. The patient expired on August 16, 1951.

Autopsy (No. L-2831) revealed the following gross findings: verrucous endocarditis, bilateral hydrothorax, ascites of 200 cc., obliterative pericarditis, fibrous pleural adhesions, enlarged kidneys, splenomegaly, generalized enlargement of lymph nodes and enlargement of adrenals.

Microscopically, there was fibrinoid degeneration in the walls of the arterioles in the heart, kidneys, bone marrow, lymph nodes and the capsules of the adrenals. In addition, there were concentric, collagenous rings of the "onion peel" variety around the central arterioles of follicles of the spleen. The capillary loops of the glomeruli of the kidneys showed thickening. The cells of the glomeruli and of Bowman's capsule were swollen and increased in number. The lymph nodes displayed advanced depletion of the lymphocytes in the medullary cords and were swollen due to the distention of sinusoids and pulp by edema fluid. The bone marrow was moderately hypoplastic. The tremendous adrenals exhibited extreme rarefaction of the cortical cells, especially of the zona fasciculata. There were large areas of necrosis except for a narrow, intact subcapsular zone. The final anatomic diagnosis was: "disseminated lupus erythematosus."

Case v. Dr. J. O. Ritchey, knowing of our interest in this phenomenon, kindly permitted us to make repeated observations on the peripheral blood of one of his private patients. This patient had been previously diagnosed as having acute disseminated lupus erythematosus, and "L.E." cells had been previously demonstrated by the Indiana University Central Laboratory, using the conventional fixed-stain technic. At the time of our examination she was on treatment with adrenocorticotrophic hormone. Supravital examinations of the peripheral blood intermittently revealed 1 to 4 per cent typical "L.E." cells. Since examination of the marrow was not possible this case is not presented in detail.

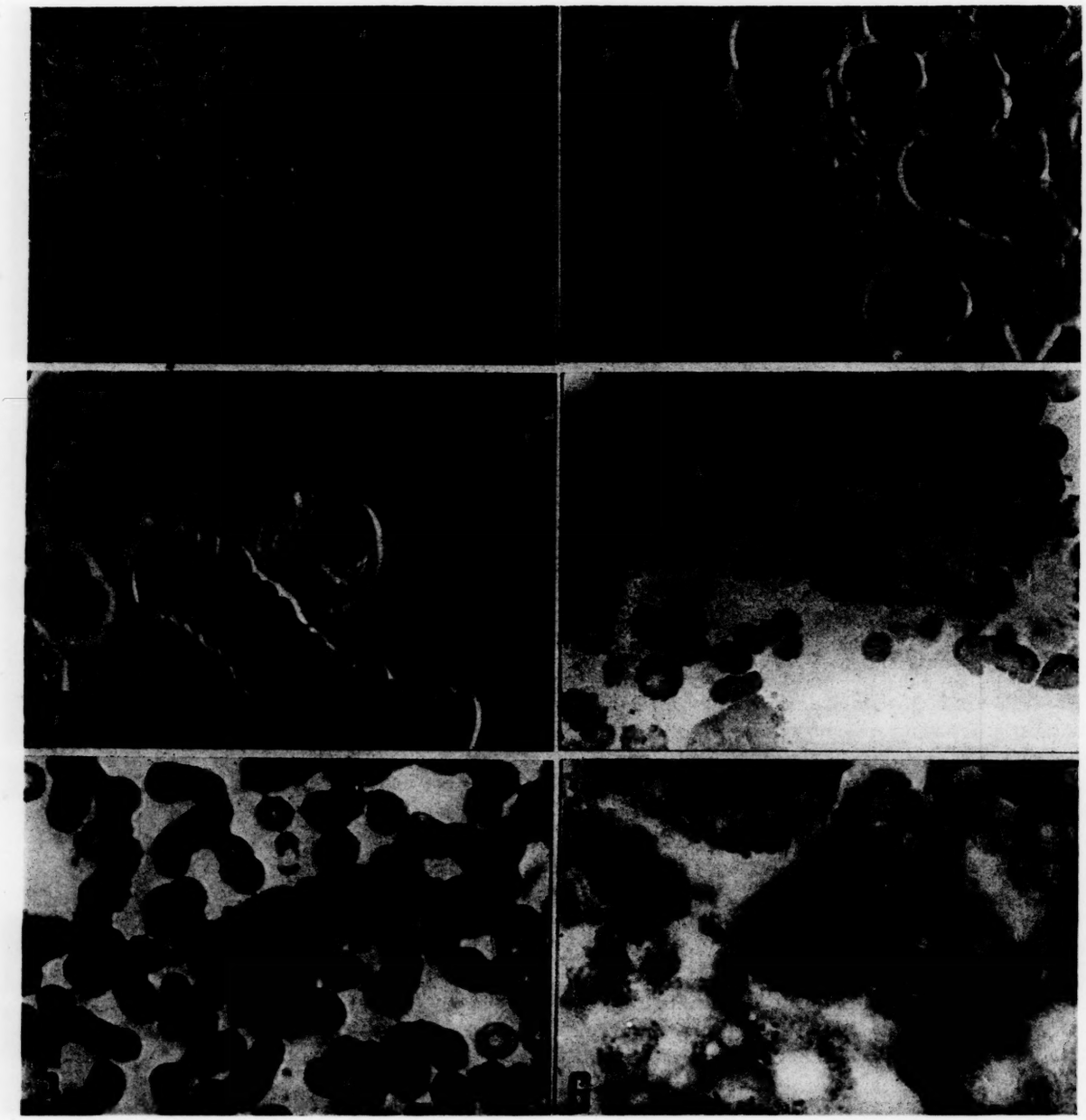


FIG. 1. Stages of nuclear autolysis in polymorphonuclear neutrophils preceding formation of "L.E." cells from Case III. A, nuclear swelling with initial accentuation of chromatin structure; B, disintegration of nuclear chromatin; C, conversion of cell into amorphous, colorless mass still retaining some specific neutrophilic granules. Supravital stain × 900.

FIG. 2. "L.E." cell from Case IV showing colorless, amorphous inclusion body. Supravital stain × 900.

FIG. 3. "L.E." cell from Case IV, later stage showing very dense, shrunken inclusion body. Supravital stain × 900.

FIG. 4. "L.E." cell from Case I. Wright stain × 900.

FIG. 5. Clump of "L.E." cells from Case II. Wright stain × 900.

FIG. 6. "L.E." cell from Case III. Wright stain × 900.

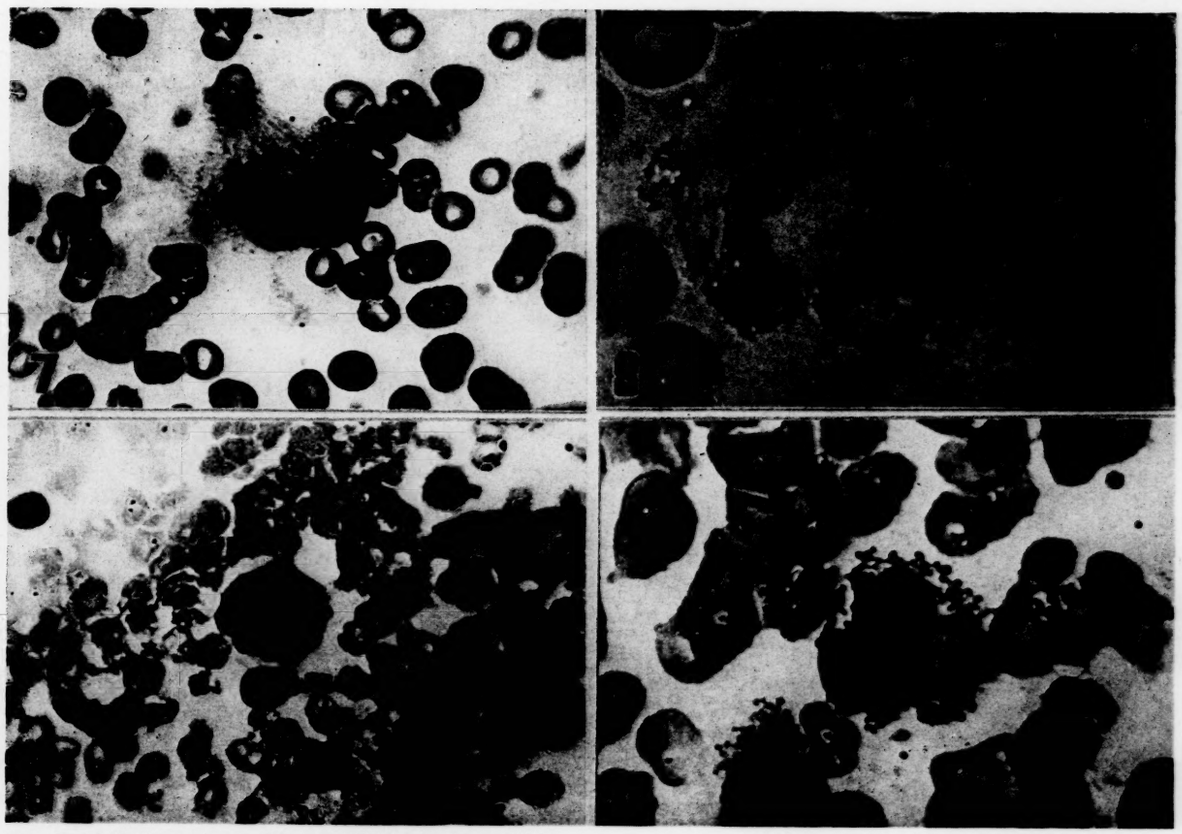


FIG. 7. "L.E." cell from Case IV. Wright stain × 900.
FIG. 8. Rosette formation with amorphous mass surrounded by polymorphonuclear neutrophils and one eosinophil (on extreme left) from Case III. Supravital stain × 900.
FIG. 9. Eosinophil containing amorphous "L.E." inclusion body from Case II. Wright stain × 900.
FIG. 10. Eosinophil containing dense, deeply stained "L.E." inclusion body from Case II. Wright stain × 900.

COMMENT

The senior author, while associated with the hematology service at the Ohio State University Medical Center, was privileged to examine the peripheral blood and bone marrows of several patients who, on the basis of clinical course and/or necropsy findings, were diagnosed as having acute disseminated lupus erythematosus. On supravital examination cells which were the supravital counterpart of fixed-stain "L.E." cells were seen in abundance. Because of difficulty in obtaining fixed-stain representation at that time these observations were not reported. We now have a simple, reliable method for obtaining permanent specimens of these cells which will be elaborated later in this discussion.

On supravital examination the following steps in the formation of the "L.E." cell have been observed. The first change noted will be seen to occur in isolated, mature, polymorphonuclear neutrophils. The nuclei of these cells will, at first, show "moist-appearing" nuclear swelling with initial accentuation of the chromatin structure. (Fig. 1A.) The nuclear membrane then becomes hazy and the nuclear chromatin structure begins to disintegrate. (Fig. 1B.) Ultimately, the cell is converted to an amorphous, colorless mass, retaining some specific neutrophilic granules with partial or complete preservation of the cytoplasmic membrane. (Fig. 1C.) When autolysis is complete, one or several mature, intact granulocytes move toward this cell and engulf it. Thus we have on direct observation confirmed the findings made by Lee et al.[6] who utilized serial, fixed-stain preparations. The advantage in this direct technic is that individual cells can be followed through the complete process.

In supravitally-stained preparations the "L.E." inclusion body is at first colorless, amorphous and faintly translucent (Fig. 2) and contains not only the disrupted nuclear contents but the cytoplasm and granules of the autolyzed cell as well. The inclusion body can then be

observed to shrink and assume a faint pink coloration. Later this structure becomes very dense and shrunken, and its coloration deepens to a deep orange red. (Fig. 3.)

When "L.E." cell formation is at a peak, permanent preparations can be easily obtained by rapidly and gently pulling the coverslip from the slide. The dried specimens can then be stained by any desired method. Wright-stained preparations, using this technic, are here illustrated. (Figs. 4 to 7.)

Mature neutrophilic, eosinophilic and basophilic polymorphonuclear leukocytes phagocytizing the "L.E." cell inclusion bodies have been observed by us. Polymorphonuclear eosinophils showing "L.E." formation are illustrated in supravital (Fig. 8) and Wright-stained (Figs. 9 and 10) preparations. We unfortunately have no available photographic representation of observed basophilic granulocyte "L.E." cells. It should be emphasized that the great majority of cells showing phagocytosis in the "L.E." phenomenon will be mature polymorphonuclear neutrophils. Supravital staining is a very sensitive delineator of the monocytic series and in our studied cases there has always been abundant monocytic representation, in the marrow specimens especially. We have in no instance, however, observed monocytes participating in "L.E." cell formation.

Repeated, careful examinations of our cases have failed to reveal any evidence of lymphocyte autolysis or phagocytosis of either intact or autolyzed lymphocytes, even though late stage, dense "L.E." cell inclusion bodies, when examined by fixed-stain methods, resemble lymphocytes or lymphocyte nuclei. We have also not yet observed megakaryocyte or platelet débris participating in "L.E." cell formation.

It might be pertinent at this point to discuss some possible sources of error in identifying the "L.E." cell by supravital technics.

Polymorphonuclear Neutrophilic Vacuolization. In systemic toxemias of any etiology neutrophilic and monocytic vacuolization may occur. These vacuoles singly or in clusters have a faint yellow or light pink coloration. While these vacuoles may assume fair size, they can be distinguished from "L.E." cell inclusions in that they are never seen to distend the cell and give the typical "signet-ring" appearance of the "L.E." cell.

Cellular Autolysis. Supravital preparations of normal peripheral blood and bone marrow, allowed to stand for a considerable period of time, will demonstrate nuclear autolysis as one manifestation of cellular death. This process is often accelerated in systemic toxemias of any etiology and by mechanical trauma in the form of increased environmental heat or undue pressure upon the coverslip. The unique features of the "L.E." cell phenomenon are, then, the rapidity and frequency of nuclear autolysis and the remarkable phagocytosis of these autolyzed cells. The chemotaxis displayed by these autolyzed cells for the phagocytizing granulocytes seems to be exclusive to the "L.E." cell phenomenon and does not occur in the usual preparation even though leukocytic autolysis might have occurred.

Phagocytosis. Polymorphonuclear neutrophils will normally cluster around, and often phagocytize, any type of foreign particulate material *in vitro*. This raises a question as to the validity of results obtained when utilizing foreign cells or other particulate foreign substances in studying the "L.E." phenomenon. In acquired hemolytic anemias, granulocytes and monocytes can be seen phagocytizing homologous or transfused erythrocytes. Under ordinary circumstances, however, no confusion should arise in differentiating phagocytized erythrocytes from "L.E." cell inclusion bodies.

Associated hematologic findings are worthy of mention. The peripheral leukopenia in acute disseminated lupus erythematosus has been frequently observed. In addition we have noted the frequent appearance in the peripheral blood of young irritation-type lymphocytes, neutrophilic myelocytes and young, stimulated monocytes. The bone marrow has invariably demonstrated acute toxic changes with many young plasma cells, clasmatocytes actively phagocytic, stimulated monocytes and young irritation lymphocytes. These findings in peripheral blood and bone marrow are most prominent in those patients whose course is unmodified by steroid therapy. While these findings may be noted in any acute, severe systemic toxemia, they arouse suspicion as to the possibility of finding "L.E." cells.

Some points in the case presentations merit particular consideration. It should be emphasized that at no time were the peripheral bloods or bone marrows of these patients handled in any other than a routine manner. The preparations were obtained, rimmed with vaseline, and read 20 to 120 minutes after preparation. The

timing is ideal for the development of the "L.E." phenomenon and in every instance supravitally stained bone marrow preparations showed a much greater representation of "L.E." cells than could be observed in our fixed-stain specimens.

It is recognized, of course, that the "L.E." phenomenon can be studied using the same technic in the absence of any stain. Absence of stain, however, makes accurate cytologic study much more difficult and is not practicable for the routine study of peripheral and bone marrow preparations.

It should be noted that in Cases I, II and III the diagnosis of acute disseminated lupus erythematosus was not clinically suspected. It was only after routine bone marrow examination had revealed considerable numbers of "L.E." cells that the diagnosis of disseminated lupus without skin manifestations was made. In these cases considerable time might have elapsed before clinical suspicion would have led us to employ any special technics for demonstrating "L.E." cells.

Case IV from the first presented a classical clinical picture of acute disseminated lupus erythematosus, and this diagnosis was substantiated by gross necropsy findings. Cases I and II, subsequent to the finding of "L.E." cells, have shown characteristic clinical features of acute disseminated lupus erythematosus, including skin eruptions with butterfly type of distribution. As of this writing Case III has not been definitely proven to be a case of acute disseminated lupus erythematosus. If and when such a diagnosis is established, it will be made the subject of a future case report.

It is interesting to note that Cases I, III, IV and V demonstrated the "L.E." cells on routine supravital differential counts of the peripheral blood, at some time, or frequently, during the course of their illness, but the number of "L.E." cells was in Cases I, III and IV always considerably less than in the bone marrow. The relationship of marrow to peripheral "L.E." cells is not known in Case V. More intensive study of these peripheral bloods might have given a higher or more frequent incidence of this finding. We do not, however, advocate the peripheral blood demonstration of "L.E." cells to the exclusion of bone marrow examination in the search for "L.E." cells. The ease and simplicity of the bone marrow examination and the greater accuracy of this method make it the technic of choice in the attempt to find "L.E." cells.

In Cases III and IV therapy with adrenocorticotrophic hormone resulted in marked diminution or disappearance of "L.E." cells from the peripheral blood and bone marrow. In Case III reduction of adrenocorticotrophic hormone below the therapeutic level resulted in reappearance of "L.E." cells in the bone marrow even before the return of any manifest symptomatology. In such a small series of cases it is unwarranted to arrive at any conclusions as to adrenocorticotrophic hormone effect or specificity of the "L.E." cell phenomenon for acute disseminated lupus erythematosus.

SUMMARY

1. We have reviewed the current literature on the "L.E." cell phenomenon, the reported methods for demonstrating these cells and the opinions as to the component parts of this phenomenon.

2. We have presented our method for obtaining, preparing and supravitally staining peripheral blood and bone marrow specimens, and five cases demonstrating the "L.E." phenomenon are summarized.

3. In our studied cases the "L.E." cell has two component parts. The "L.E." cell inclusion body has invariably been a mature, autolyzed polymorphonuclear neutrophil. The phagocytic cell, in our experience, has been shown to be either a mature polymorphonuclear neutrophilic, eosinophilic or basophilic leukocyte, with the neutrophilic leukocytes overwhelmingly predominating.

4. Bone marrow examination is the most reliable means of demonstrating "L.E." cells by our technic even though we have, on routine peripheral blood examination, found "L.E." cells present in four of the five summarized cases.

5. We present this as a simple, effective, direct method for demonstrating "L.E." cells without resorting to special manipulative procedures of peripheral blood or bone marrow.*

REFERENCES

1. Hargraves, M. M., Richmond, H. and Morton, R. Presentation of two bone marrow elements: the

* *Addendum:* Since the submission of this manuscript for publication on reviewing a fixed stain preparation from Case II, we found one phagocytic clasmatocyte containing what appears to be a typical "L.E." inclusion body. We have not been able to confirm this observation on repeated supravital examinations.

"tart" cell and the "L.E." cell. *Proc. Staff Meet., Mayo Clin.*, 23: 25–28, 1948.

2. Haserick, J. R. and Sundberg, R. D. The bone marrow as a diagnostic aid in acute disseminated lupus erythematosus. *J. Invest. Dermat.*, 11: 209–213, 1948.
3. Hargraves, M. M. Cited by Montgomery, H. and MacCreight, W. G. Disseminated lupus erythematosus. *Arch. Dermat. & Syph.*, 60: 356–372, 1949.
4. Berman, L., Axelrod, A. R., Goodman, H. L. and McClaughry, R. I. So-called "lupus erythematosus inclusion phenomenon" of bone marrow and blood. *Am. J. Clin. Path.*, 20: 403–418, 1950.
5. Kurnick, N. B. Cited by Lee, S. L., Michael, S. R. and Vural, I. K.[6]
6. Lee, S. L., Michael, S. R. and Vural, I. L. The L.E. (lupus erythematosus) cell. *Am. J. Med.*, 10: 446–451, 1951.
7. Haserick, J. R., Lewis, L. A. and Bortz, D. W. Blood factor in acute disseminated lupus erythematosus. I. Determination of gamma globulin as specific plasma fraction. *Am. J. M. Sc.*, 219: 660–663, 1950.
8. Haserick, J. R. and Lewis, L. A. Blood factor in acute disseminated lupus erythematosus. II. Induction of specific antibodies against L.E. factor. *Blood*, 5: 718–722, 1950.
9. Moyer, J. B. and Fisher, G. S. Experimental production of "L.E." cells. *Am. J. Clin. Path.*, 20: 1011–1015, 1950.
10. Lee, S. L., Michael, S. R. and Vural, I. L. The lupus erythematosus ("L.E." cell). *Bull. New York Acad. Med.*, 26: 266, 1950.
11. Hargraves, M. M. Production in vitro of the L.E. cell phenomenon: use of normal bone marrow elements and blood plasma from patients with acute disseminated lupus erythematosus. *Proc. Staff Meet., Mayo Clin.*, 24: 234–237, 1949.
12. Lee, S. L. A simple test for L.E. cells. *Am. J. Clin. Path.*, 21: 492–496, 1951.
13. Eppes, W. and Ludovic, E. Demonstration of the "L.E." cell without use of anticoagulants. *Blood*, 6: 466–469, 1951.
14. Haserick, J. R. and Bortz, D. W. Normal bone marrow inclusion phenomena induced by lupus erythematosus plasma. *J. Invest. Dermat.*, 13: 47–49, 1949.
15. Haserick, J. R. and Bortz, D. W. A new diagnostic test for acute disseminated lupus erythematosus. *Cleveland Clin. Quart.*, 16: 158–161, 1949.
16. Moffatt, T. W., Barnes, S. S. and Weiss, R. S. Induction of the L.E. cell (Hargraves) in normal peripheral blood. *J. Invest. Dermat.*, 14: 153–156, 1950.
17. Sabin, F. R. Studies of living human blood-cells. *Bull. Johns Hopkins Hosp.*, 34: 277–288, 1923.

The Effectiveness of Various Drugs for the Prophylaxis of Seasickness*

MAJ. HERMAN I. CHINN, M.S.C., U.S.A.F., LT. COMDR. STANLEY W. HANDFORD, M.S.C., U.S.N., COMDR. THOMAS E. CONE, JR., M.C., U.S.N.
and LT. COL. PAUL K. SMITH, U.S.A.F.
Washington, D. C.

At the recent conference on motion sickness sponsored by the Office of Naval Research the attending investigators in this field were in complete agreement that screening procedures for anti-motion sickness drugs are urgently needed.[1] The exact mechanism by which protection against motion sickness is achieved is not known and no completely satisfactory drug is now available. However, compounds with pharmacologic properties similar to known effective agents must be considered and tested for possible prophylactic efficacy. Further, field studies under actual military conditions must be greatly expanded in order to obtain definite evidence of the possible value of a particular preparation. The usefulness of tests on troops aboard military transports has been convincingly shown;[2] during a single transatlantic crossing and return ten preparations and dosage schedules were tested in addition to the necessary control group.[3]

Although certain antihistaminic drugs exert considerable protection, prophylaxis against motion sickness does not depend upon the antihistaminic action of the drug. Thus pyranisamine (neoantergen) maleate and phenindamine (thephorin) tartrate are ineffective in doses eliciting strong antihistaminic action.[3] The effectiveness of dimenhydrinate (dramamine), diphenhydramine (benadryl) hydrochloride and chlorcyclizine (perazil) hydrochloride must therefore be attributed to other pharmacologic properties.[3] Their anticholinergic action seems the most plausible since other drugs with central atropine-like action such as scopolamine hydrobromide and trihexyphenidyl (artane) possess similar prophylactic properties.

This report is of the continuation of tests on drugs of possible value through a cooperative study by the Army, Navy and Air Force. Subjects were drawn from all three services; the transports were supplied by the Military Sea Transport Service, United States Navy, while the supervisory and assisting personnel were from both the Navy and Air Force. The preparations tested were selected for a variety of reasons. Diphenydramine† was chosen as a control drug because of its known value as a protective.[3] A mixture of diphenydramine and scopolamine has been the most effective remedy against airsickness[4,5] but had not been given a trial against seasickness. Similarly, scopolamine aminoxide hydrobromide (scopodex)‡ and the scopolamine aminoxide-diphenhydramine mixture give significant protection against airsickness[4,5] but had not been tested at sea. Preliminary studies by MacKay[6] with the antihistaminic prophenpyramine (trimeton)§ maleate against airsickness were promising. A long-acting antihistaminic, N (α methyl β dimethyl aminoethyl) phenothiazine hydrochloride (lergigan)‖[7] has been

† Benadryl (beta-dimethylaminoethyl benzhydryl ether hydrochloride) and the benadryl-scopolamine mixture were supplied by Parke, Davis & Co., Detroit, Mich.

‡ Scopodex (scopolamine aminoxide hydrobromide) and the benadryl-scopodex mixture were supplied by Lobica-Debruille, Inc., New York, N. Y.

§ Trimeton (1 phenyl-1-(2-pyridyl)-3-dimethyl-aminopropane) was supplied by Schering Inc., Bloomfield, N. J.

‖ Lergigan (N(α-methyl β-dimethyl aminoethyl) phenothiazine hydrochloride) was supplied by A. B. Recip Co., Stockholm, Sweden.

* From the Department of Pharmacology, U.S.A.F. School of Aviation Medicine, Randolph Field, Tex., the Department of Physiology, Naval Medical Field Research Laboratory, Camp LeJeune, N. C., Military Sea Transport Service, Atlantic, Brooklyn, N. Y., and Department of Pharmacology, The George Washington University School of Medicine, Washington, D. C. Tri-Service Medical Department Cooperative Study, Department of Defense. The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Department of Defense.

reported to protect against seasickness. Furthermore, it is known to prevent the compulsive turning of animals after intracarotid injection of diisopropyl fluorophosphate (DFP), a property possessed by certain other effective anti-motion sickness drugs.[8] N-benzhydryl N methyl piperazine dihydrochloride (preparation 47–83)* was chosen because of its close chemical similarity with chlorocyclizine (perazil), which has been shown to afford significant protection against both air[5] and seasickness.[3] Methaphenilene (diatrin) hydrochloride, another antihistamine, and β diethylamino ethyl-2-thienyl (α-2-cyclopentenyl) acetate hydrochloride (preparation W-290), an antispasmodic, have each been reported to give some protection against the emesis following apomorphine injection.[9]† The strong anticholinergic properties of 1,1-diphenyl N,N-dimethyl 4-piperylidene methane methyl sulfate (prantal) suggested that it be included.[10]‡

EXPERIMENTAL STUDIES

Two Military Sea Transport Service ships were employed during their routine crossings from New York to Bremerhaven, Germany, and return. The General R. E. Callan, a C-4 type vessel with a full load displacement of 16,750 tons, sailed on February 1, 1951, and arrived in Bremerhaven on February 11th. It departed from Bremerhaven on February 12th and returned to New York on February 23rd. The General Alexander Patch is a somewhat larger ship with a full load displacement of 22,379 tons. It departed on February 27th, arrived in Bremerhaven on March 9th, departed Bremerhaven March 11th and returned to New York March 21st.

Only male volunteer subjects were employed on both ships. Abroad the General Callan troops were quartered on two levels, on E and F decks, in five compartments near the center of the ship. The number of troops in each compartment varied from 124 to 233. Prior to sailing a questionnaire was completed on each man to determine his age, previous history of motion sickness, sailing and flying experience. The median age was twenty-two years with 69.6 per cent of the subjects younger than twenty-five years and 86.6 per cent below thirty. Approximately half the men on the outward trip were making their first ocean crossing and 36.9 per cent of the remainder had been seasick previously. The incidence of sickness from riding in airplane, car, train or amusement park devices was low. There was no significant difference in the distribution of these motion-susceptible individuals insofar as subsequent medication was concerned. As in the previously reported study,[3] the subjects were divided at random into seven groups. Subjects receiving each drug were randomly distributed in each compartment. The groups received, respectively, the following: (1) placebo; (2) diphenhydramine hydrochloride, 50 mg.; (3) diphenhydramine hydrochloride, 25 mg. scopolamine hydrobromide, 0.35 mg.; (4) lergigan, 25 mg.; (5) prophenpyramine maleate, 25 mg.; (6) methaphenilene hydrochloride, 50 mg.; and (7) W-290, 50 mg. All preparations were given in pink capsules of identical size and appearance. The first capsule was given at 2:00 P.M., approximately one hour before sailing, at 9:00 P.M., that evening and at 6:00 A.M., 11:00 A.M. and at 6:00 P.M. (immediately before each meal) for the next two days, a total of eight capsules. All medicaments were swallowed immediately under observation. Because of the long duration of action reported for lergigan a placebo was substituted for the drug during the 11:00 A.M. distribution so that only two capsules (50 mg.) were given daily. Each subject was questioned daily and, if vomiting occurred, the exact time was recorded. In addition, a questionnaire was obtained from each man indicating the incidence and time of vomiting or nausea and any side effects attributable to the drug. A total of 689 subjects completed the test.

To permit correlation of the movements of the ship with the incidence of vomiting a pitch and roll recorder, constructed by the Material Laboratory, New York Naval Shipyard, was installed at the approximate center of gravity. The roll and pitch were recorded continuously, and the linear and angular accelerations in the different compartments were calculated from the pitching and rolling amplitudes and periods. It was assumed that the axis of roll was in the longitudinal plane of symmetry and the axis of

* Preparation 47–83 (N-benzhydryl N'methyl piperazine dihydrochloride) was supplied by the Wellcome Research Laboratories, Tuckahoe, N. Y.

† Diatrin (N, N-dimethyl N'phenyl-N'(2-thienyl methyl) ethylene diamine hydrochloride) and W-290 (β diethylamino ethyl-2-thienyl (2-cyclopentenyl) acetate hydrochloride) were supplied by William R. Warner & Co., N. Y.

‡ Prantal (1,1-diphenyl N,N-dimethyl 4-piperylidene methane methyl sulfate) was supplied by Schering Corporation, Bloomfield, N. J.

pitch was located on the waterline about two-thirds of the length from the bow.

Aboard the General Patch all subjects were quartered at the same level (C deck). Five compartments were utilized, containing from 72 to 158 men each. The age distribution was approximately the same as aboard the General Callan. The median age was again twenty-two years, with 73.5 per cent below twenty-five years of age and 88.9 per cent younger than thirty years. Approximately half (45.0 per cent) had made a previous crossing and 38.8 per cent of these had been seasick before. A total of 591 subjects completed the test. The preparations tested during this crossing were: (1) placebo; (2) diphenhydramine, 50 mg.; (3) scopolamine aminoxide hydrobromide, 2.0 mg.; (4) scopolamine aminoxide hydrobromide, 1.0 mg.—diphenhydramine hydrochloride, 25 mg.; (5) preparation 47–83, 50 mg.; and (6) methyl pyridphen methyl sulfate, 50 mg.

The schedule for administering the capsules was the same as already described except that a total of six were given instead of the eight distributed aboard the General Callan.

TABLE I

EFFECTIVENESS OF VARIOUS DRUGS AGAINST SEASICKNESS

Drug	Dosage (mg., t.i.d.)	No. of Subjects	Vomiting (per cent)	P	Protection† (per cent)
		Aboard General Callan			
Placebo	....	100	38.0	....	....
Benadryl	50.0	103	17.5	<0.01	53.9
Benadryl–Scopolamine	25.0 0.35	93	16.1	<0.01	57.6
Lergigan	25.0*	99	11.1	<0.01	70.8
Trimeton	25.0	100	15.0	<0.01	60.5
Diatrin	50.0	95	44.2	>0.20	....
W-290	50.0	99	43.4	>0.20	....
		Aboard General Patch			
Placebo	....	101	37.6	....	....
Benadryl	50.0	99	14.2	<0.01	62.2
Scopodex	2.0	96	24.0	0.04	36.2
Benadryl–Scopodex	25.0 1.0	96	26.0	0.09	30.9
Wellcome 47-83	50.0	106	17.0	<0.01	54.8
Prantal	50.0	93	34.4	>0.20	8.5

*Two times daily.

†Per cent vomiting in placebo group minus per cent vomiting in drug group, divided by per cent vomiting in placebo group X 100.

RESULTS

The incidence of vomiting among the various groups is given in Table I. Although mild and severe nausea were also recorded, these data are not included because of their subjective nature. No subject is included in this series who did not take the capsule administered before sailing regardless of its content or his subsequent reaction. Similarly, no subject was included who missed the capsule immediately prior to vomiting. Again, no distinction was made between placebo or other medication. The probability was determined by means of the chi square test.

During the General Callan crossing the maximum pitch for the period covered by Table I was 4.5 degrees at 4:00 A.M. of the first night. The period of pitch was between seven and ten seconds. The maximum roll, which occurred at approximately the same time, was 18.5 degrees with a period of 14.9 seconds. Most of the vomiting resulted during this period of greatest turbulence. The maximum linear accelerations in the compartments varied from 4.95 to 6.45 feet/second^2. The angular accelerations were approximately 3 degrees/second^2. During the General Patch crossing the maximum pitch was 4.8 degrees at 8:00 A.M. on the morning of the third day, shortly after the last capsule was given. The period of the pitch averaged 9.2 seconds. The maximum roll occurred at 2 A.M. on the third day and was 12.5 degrees with a period of 13.3 seconds. The highest incidence of nausea and vomiting occurred on this morning. An attempt was made to correlate the incidence of sickness in each compartment with the acceleration to which the subjects in that compartment were exposed. No significant correlation could be detected. Since resistance during sleep is considerably increased and since relatively little of the waking time was spent in the compartments, these results are not surprising.

Table II

Effect of Age on Sickness

Age	No. of Subjects	Vomiting (per cent)
17–20	238	33.6
20–24	655	28.1
25–29	211	18.5
30–39	134	14.2
> 40	16	25.0

Significant protection at the 1 per cent probability level was obtained with benadryl during both crossings, with lergigan, trimeton and the benadryl-scopolamine mixture aboard the General Callan and with preparation 47–83 aboard the General Patch. Scopodex also afforded significant protection although at a lower probability level (5 per cent). The decrease in vomiting with the benadryl-scopodex mixture is suggestive but does not represent a statistically significant difference from the placebo group. No protection whatever was afforded by diatrin, W-290 and prantal. The incidence of vomiting was least with lergigan, but neither it nor the other protective drugs differed significantly from benadryl. More extensive studies are necessary for any definitive evaluation of these drugs. It is interesting to note that the protection afforded by benadryl on the two trips was 54 and 62 per cent, respectively, compared with 60 per cent on the previously reported study.[3] The consistency of these values under varying conditions is encouraging. No essential difference from Table I was evident when the effectiveness of the various drugs was determined among known susceptibles, i.e., those who had reported previous motion sickness whether in a ship, car, airplane, train or amusement device. The same drugs showed protection, with lergigan again apparently the best.

It has been widely reported that infants and elderly people are more resistant to motion sickness than individuals in the middle age groups.[11–16] We have been unable, however, to find any quantitative data in support of this impression. Our subjects fell within a rather narrow age zone but showed, nevertheless, a decreased susceptibility to seasickness as they grew older. The series of men over forty was so small that it should be disregarded. It must be remembered that the subjects were quartered in different compartments and received different medication. However, since the age distribution did not vary significantly for drug or compartment, it is believed that Table II represents a true increase in resistance with age. Furthermore, consideration of the placebo group alone shows a similar age distribution although the individual series are too small for statistical evaluation. It would be desirable to extend this series.

As pointed out before, it is extremely difficult to differentiate certain possible side effects of the drug from symptoms induced by motion or the altered environmental conditions aboard ship. The side effects reported are shown in Table III. None of the preparations tested aboard the General Callan produced a significant increase in any symptom recorded. The most common complaint was drowsiness but, as is

evident in Table III, subjects receiving benadryl, lergigan and trimeton despite their reported sedative action had, if anything, a somewhat lower incidence than with placebo. It is interesting that the benadryl-scopolamine mixture produced no increase in blurred vision or dry mouth. With the usual dose of scopolamine-hydrobromide (0.65 to 0.75 mg.) a considerably increased incidence of both of these symptoms has been reported.[3]

TABLE III

PER CENT SIDE EFFECTS OF DRUGS ADMINISTERED

Drug	Drowsiness	Insomnia	Nightmares	Blurred Vision	Dry Mouth	Tinnitus	Headache
			Aboard General Callan				
Placebo	41.7	24.1	1.9	14.8	32.4	3.7	41.7
Benadryl	31.9	3.5	0	11.5	26.5	4.4	29.2
Benadryl–Scopolamine	31.4	20.0	0	10.5	37.1	3.8	27.6
Lergigan	37.3	11.8	0	6.9	19.6	4.9	32.4
Trimeton	34.9	10.4	0	10.4	25.5	1.9	30.2
Diatrin	48.5	12.9	0	10.9	19.8	1.0	43.6
W-290	43.4	13.2	3.8	10.5	33.0	4.8	36.2
			Aboard General Patch				
Placebo	44.1	16.2	9.9	20.7	31.5	4.5	43.2
Benadryl	43.6	10.9	5.5	27.3	29.1	4.5	39.1
Scopodex	47.4	23.7	24.6*	64.0*	65.7*	15.8*	38.6
Scopodex–Benadryl	53.6	25.0	15.2	55.4*	57.1*	8.9	39.3
Wellcome 47-83	40.4	14.0	2.6	21.1	28.9	4.4	37.7
Prantal	46.4	19.1	7.3	26.3	34.5	9.1	45.5

*Significant at 1 per cent probability level.

Among the second group of drugs tested the most striking and alarming symptom was the high incidence of nightmares and hallucinations among those receiving 2 mg. of scopodex. Approximately one-quarter (24.6 per cent) of all subjects who received scopodex reported nightmares. Eleven men in this group suffered hallucinations and one became manic. Symptoms appeared generally after the third dose of scopodex and lasted from twenty-four to thirty-six hours. The incidence of blurred vision, dry mouth and tinnitus were extremely high, several times greater than the placebo in most cases and invariably higher than any other group. When the dosage of scopodex was reduced to 1.0 mg. (plus 25 mg. benadryl), the incidence of these side reactions dropped in every case although they remained higher than the placebo group. Thus there was still a significant increase in blurred vision and dry mouth and an apparent increase in nightmares and tinnitus. No case of hallucinations was noted. Insomnia was increased in both scopodex groups although in neither case was this increase statistically significant.

COMMENT

Of the various preparations demonstrated to have significant protection against seasickness in the present as well as our previous study[3] lergigan appears to be the most promising, not only because of an apparently greater protection but also because of its long duration of action. This latter property would be especially valuable in long sea voyages during which frequent medication may be harmful as well as inconvenient. Additional studies are urgently needed to confirm and extend these observations. Trimeton and compound No. 47–83 also gave promise and should be tested further. Scopodex alone at the 2.0 mg. level gave significant protection but

produced such numerous and serious side effects that its use is impractical. At the lower dosage level (with benadryl) the protection was not significant. Although it has been reported that scopodex is only one-sixth as toxic as scopolamine and that its duration of action is short, neither claim was in harmony with our findings. Thus 2.0 mg. of scopodex produced far more severe reactions than had 0.75 mg. of scopolamine hydrobromide.[3] In fact, the incidence of anticholinergic reactions among those receiving only 1.0 mg. of scopodex plus benadryl was high. The fact that hallucinations appeared after the third dose and that the symptoms increased in number and severity with continued dosage points to a cumulative action of the drug. Since only three doses were given daily, the duration of action must be relatively long. In these doses the toxicity and duration of action of scopodex were at least as great as those of scopolamine hydrobromide in doses of 0.75 mg.[3]

The ineffectiveness of diatrin provides further evidence that motion sickness prevention is not closely associated with the antihistaminic action of these drugs. Similarly, the failure of W-290 and prantal eliminates any general anticholinergic action as the responsible effect. A central anticholinergic action is still possible since lergigan, as well as several other effective motion sickness preventives, has been shown to prevent the convulsions produced by intracarotid injections of an anticholinesterase (DFP) as well as the forced circling movements simultaneously produced.[8] It would be of interest to test anticholinergic compounds which do not protect against motion sickness by this forced circling technic.

SUMMARY AND CONCLUSIONS

N (α-methyl β-dimethyl aminoethyl) phenothiazine hydrochloride (lergigan), prophenpyridamine (trimeton), diphenhydramine (benadryl) hydrochloride, scopolamine hydrobromide mixture, and N-benzhydryl N'methyl piperazine dihydrochloride (preparation No. 47–83) all provided approximately equal protection against seasickness. No preparation was significantly superior to that of diphenhydramine although the observed per cent protection afforded by lergigan was slightly greater.

No protection was given by the antihistaminic methaphenilene (diatrin), or by the antispasmodic β-diethylamino ethyl-2-thienyl (α 2-cyclopentenyl) acetate hydrochloride (W-290) or methylpyridphenmethyl sulfate (prantal). Slight protection, not significant at the 1 per cent level, was obtained with scopodex alone or with a mixture of diphenhydramine and scopolamine aminoxide.

Side effects were minimal in all cases except among those persons receiving the scopolamine aminoxide. When 2.0 mg. doses of the latter were given three times daily, hallucinations, an increased incidence of nightmares, dry mouth, blurred vision and ringing in the ears were observed. When 1.0 mg. was given combined with 25 mg. of diphenhydramine, there were no hallucinations but the incidence of nightmares, dry mouth and blurred vision was still increased.

There was an inverse relation between the incidence of vomiting and the age of the subject. No relation could be detected between the number sick and the compartments in which they were quartered nor with the degree and/or duration of motion therein under the conditions of these sea trials.

Acknowledgment: The following persons contributed largely to this study: Capt. C. C. Shaw (M.C.) U.S.N., Director, Research Division, Bureau of Medicine and Surgery, Washington, D. C., and Comdr. W. J. Dougherty (M.C.) U.S.N., of Military Sea Transport Service, Atlantic, procured the authorization of the use of the Naval personnel, the ships and equipment to make these trips possible and coordinated all phases of the experiment; Col. A. P. Gagge, Director of Research, Surgeon General's Office, U.S.A.F., procured the authorization for the use of Air Force personnel and aided in planning the study; Col. J. R. Wood, Surgeon General's Office, U.S.A., made available the bulk of our subjects; Capt. C. P. Archambeault (M.C.) U.S.N., and Capt. B. F. Brown (M.C.) U.S.N., of the Medical Division, Military Sea Transport Service, authorized the use of ships and key personnel; Mr. Manley St. Denis, Mr. Bruce Burnside, Mr. Sam Gover and Mr. Robert Tuckerman of the David Taylor Model Basin, U. S. Navy, Washington, D. C., installed all motion recording devices and made all measurements and calculations. Sgt. Harvey Midkiff, U.S.A.F., Cpl. Kimball K. Hemsley, U.S.A.F., H.M./2 Andrew J. Davidson, U.S.N., and H.M./3 Patsy Mata, U.S.N., gave valuable technical assistance, and Doctor Max Halpern and Cap. W. L. Dixson, U.S.A.F., of the School

of Aviation Medicine made the statistical evaluation.

REFERENCES

1. Report of Conference on Motion Sickness, Office of Naval Research, Department of the Navy, Washington, D. C., Sept. 9, 1950.
2. Gay, L. N. and Carliner, P. E. The prevention and treatment of motion sickness. I. Seasickness. *Science*, 109: 359–360, 1949; *Bull. Johns Hopkins Hosp.*, 84: 470–487, 1949.
3. Chinn, H. I., Noell, W. K. and Smith, P. K. Prophylaxis of motion sickness. Evaluation of some drugs in seasickness. *Arch. Int. Med.*, 86: 810–822, 1950.
4. Chinn, H. I., Strickland, B. A., Waltrip, O. H. and Gainer, S. H. Prevention of air sickness by benadryl-scopolamine mixtures. *U. S. Armed Forces M. J.*, 2: 401–404, 1951.
5. Chinn, H. I., Waltrip, O. H. and Massengale, H. W. Further studies on the effectiveness of various drugs against air sickness. (In press.)
6. MacKay, E. M. Personal communication.
7. Engquish, S. Ett nytt Svenskt sjössjukemedel. *Svenska Läkartidningen*, 47: 1464–1468, 1950.
8. John, R. J. and Himwich, H. E. A central action of some antihistamines. Correction of forced circling movements and of seizure brain waves produced by the intracarotid injection of di-isopropyl-fluorosphosphate (DFP). *Am. J. Psychiat.*, 107: 367–372, 1950.
9. Krop, S. Personal communication.
10. Tislow, R. Personal communication.
11. Bennett, R. A. Seasickness and its treatment. *Brit. M. J.*, 1: 752, 1928.
12. Blackham, R. J. Seasickness. *Brit. M. J.*, 2: 163, 1939.
13. Brooks, M. Seasickness. *U. S. Nav. M. Bull.*, 37: 469, 1939.
14. Oriel, G. H. The treatment of seasickness. *Lancet*, 2: 1146, 1927.
15. Humphreys, L. Seasickness. *U. S. Nav. M. Bull.*, 35: 293, 1937.
16. Desnoes, P. H. Seasickness. *J. A. M. A.*, 86: 319, 1926.

A Study of the Therapeutic Effects of Some Amebacidal Drugs*

WILLIAM A. SODEMAN, M.D. *and* PAUL C. BEAVER, PH.D.
New Orleans, Louisiana

THE possibility of comparing the effects of amebacidal drugs presented itself in the Ellisville State School for the feebleminded in Ellisville, Mississippi. In this institution during the winter and spring of 1949 to 1950 we were offered an opportunity to manage the treatment of a large group of essentially hospitalized patients in whom a high rate of infection with Endamoeba histolytica had been found, where it was possible to establish fairly rigid quarantine, to treat simultaneously all members of the hospital community and to study a series of post-treatment stools without appreciable risk of having the results altered by outside sources of infection.

Four amebacidal drugs were used, two of which were regarded as among the clinically best established and most widely used, chiniofon® and diodoquin,® and two of which were considered to be promising but relatively untried clinically, milibis® and thioarsenites.® Milibis is anarsenical-bismuth combination which was introduced by Hauer in 1943. Its composition and history have been described by Berberian, Dennis and Pipkin[1] in a recent favorable report on its clinical use. Successful trial of thioarsenites was reported by Anderson et al.[2] in 1949.

MATERIALS AND METHODS

When the study was begun, the study group consisted of approximately 350 individuals representing all age groups housed in five dormitories: two for females of all ages, two for adult males and one for juvenile and adolescent males. During the six-month study period there were nine withdrawals and thirty-three admissions, the large number of admissions being permitted by expanded facilities. As a rule, the institution's census is relatively stable because admission usually results in life-long residence. Residents of each dormitory are fed separately but food is prepared in a modern central kitchen.

Preliminary to treatment single stools of all patients and some of the attendants and kitchen employees were examined. For each inmate of one of the dormitories (B 1) three stools spaced three to eight days apart were examined. Three check-up stool examinations were made two, three and four to five weeks after treatment was completed.

One ounce tin boxes were labeled and distributed to the dormitories and matrons attended to the collection of the stool specimens. Purgation was used infrequently, mostly on invalids. Most of the collections were made from morning stools and shipment to the laboratory was made within a few hours. Late collections were held under refrigeration until the following day. Shipments were received twelve to thirty-six hours after collection and usually were examined within twenty-four hours of arrival. One or two days in advance of stool collections fatty foods and milk were eliminated from the diets in order to facilitate examination of the feces.

In addition to the routine collection samples from each of the diarrheic specimens were fixed and preserved in polyvinyl alcohol—Schaudinn's solution for special iron-hematoxylin staining as described by Brooke.[3] All specimens were concentrated by zinc sulfate centrifugal flotation and examined in iodine stain. When identifications were difficult, iron-hematoxylin stained smears were studied. If identifications were doubtful or specimens were unsatisfactory for other reasons, additional specimens were requested.

The stool survey indicated a high rate of amebic infection. After considering the nature

* From the Department of Tropical Medicine and Public Health, School of Medicine, Tulane University of Louisiana, New Orleans, La.

of the subjects, the costs involved and the probability of failure if the diagnosis and treatment were handled on an individual basis, we decided that all individuals including attendants would be given treatment simultaneously and the post-treatment checking of stools likewise would be handled on a mass rather than an individual basis. In this way failures to cure would be detected promptly and treated so that reinfection would be held to a minimum.

The drugs were given under such close supervision that very few individuals could have failed to receive the full dose regularly. The following dosages were used for adults: diodoquin, 3 tablets (0.21 gm. per tablet) three times daily for twenty days; chiniofon, 4 pills (0.25 gm. per pill) three times daily for eight days; milibis, 2 tablets (0.25 gm. per tablet) three times daily for eight days; and thioarsenites, 2 tablets (0.05 gm. per tablet) three times daily for ten days. All children were given either diodoquin or chiniofon with the dosage reduced to not less than three tablets or pills per day.

RESULTS

Reliability of Records. Of seventy-six individuals who submitted one pre- and three post-treatment specimens, there were eight whose records contained inconsistencies suggestive of mislabeling of specimens. There were nine such cases among sixty-two individuals who submitted three pre- and three post-treatment specimens. Thus of 676 specimens from this group there were less than 3 per cent that were of questionable origin.

Pretreatment Survey. As shown in Table I, results from the pretreatment survey differed considerably in the various dormitories. This was in part due to partial segregation of the subjects and contagion of their parasites but the wide variation in findings from group to group was due in part also to variation in the number of stool examinations made. E. histolytica was found in 12 to 20 per cent of those with only one stool examination whereas three examinations revealed this ameba in nearly 50 per cent of the sixty-one individuals in dormitory B 1. Another important factor in this increase of incidence is the character of the stools submitted. Normal, mushy-formed, dark, non-fatty stools obtained by control of diets contained more amebas and were more suitable for concentration by zinc sulfate flotation.

With reference to parasites other than E. histolytica, it is noteworthy that in B 1 Endolimax nana exceeded even Endamoeba coli; in B 1 and G 2 the incidence of Iodamoeba bütschlii ran especially high; hookworm infection was prevalent only among the boys (groups B 1 and B 2) who were allowed considerable out-of-doors freedom and Hymenolepis nana was confined almost entirely to the one dormitory for juvenile and adolescent boys.

TABLE I

PERCENTAGE OF INDIVIDUALS WITH VARIOUS PARASITIC INFECTIONS FOUND AS A RESULT OF SPECIFIED NUMBERS OF STOOL EXAMINATIONS PRIOR TO ANTI-AMEBIC TREATMENT

	Dormitory					
	N	B1	B2	G1	G2	All Groups
No. with 1 stool examined	46	----	66	58	87	257
No. with 2 stools examined	----	5	----	----	23	28
No. with 3 stools examined	----	56	----	----	----	56
Total individuals	46	61	66	58	110	341
Endamoeba histolytica	19.6	49.2	12.1	17.2	18.2	22.6
Endamoeba coli	54.3	72.1	30.3	43.1	70.9	56.3
Endolimax nana	21.7	77.0	24.2	17.2	56.4	42.5
Iodamoeba butschlii	8.7	24.6	7.6	10.3	25.5	17.0
Giardia lamblia	28.3	8.2	13.6	17.2	12.7	15.0
Chilomastix mesnili	----	1.6	3.0	----	3.6	2.0
Ascaris lumbricoides	----	----	1.5	----	----	----
Trichuris trichiura	----	----	1.5	----	----	----
Necator americanus	4.3	45.9	16.7	3.4	1.8	13.2
Strongyloides stercoralis	----	9.8	7.6	5.2	0.9	4.4
Enterobius vermicularis	----	11.5	1.5	----	2.7	3.2
Hymenolepis nana	17.4	1.6	----	----	----	2.6
No parasites found	23.9	8.2	31.8	27.6	9.1	18.5

Results of Treatment. When treatments were begun, there was a certain amount of selection of individuals in order to give the two experimental drugs the more severe tests and to facilitate administration of the treatments. A new dormitory (G 3) was opened to relieve overcrowding in G 1 and G 2. All of the twenty-nine individuals who were given thioarsenites were in G 3 and twelve others in the same group were given diodoquin along with all of dormitory N. Milibis was given to all of B 1 and G 1 and to selected cases from B 2. The remainder (G 2 and part of B 2) were given chiniofon.

The number in each treatment group together with the results of pre- and post-treatment stool examinations are shown in Table II. E. histolytica was found after treatment in only two individuals, both in dormitory B 2 and both had been given the full course of chiniofon. E. coli and the other non-pathogenic amebas apparently were eliminated in the group treated with

thioarsenites. E. coli was nearly eradicated by milibis and diodoquin while chiniofon merely reduced the incidence from 55 per cent to 20 per cent. E. nana was unaffected by chiniofon and diodoquin but was very significantly reduced by milibis. I. bütschlii survived treatment only in the group given chiniofon and even here there was a reduction from twenty-six to only four known infections.

TABLE II

FINDINGS ON 341 INDIVIDUALS TREATED WITH CHINIOFON, DIODOQUIN, MILIBIS, THIOARSENITES, PRECEDED BY 1-3 AND FOLLOWED WITH 3 STOOL EXAMINATIONS THAT WERE MADE 2, 3 AND 4-5 WEEKS AFTER TREATMENTS WERE COMPLETED

Drug Used	No. in Group	No. with 1, 2 or 3 Pretreatment Stool Examinations			Per Cent Positive Before and After Treatment								Per Cent Negative for All Amebas	
					E. histolytica		E. coli		E. nana		I. bütschlii			
		1	2	3	Before	After	Before	After	Before	After	Before	After	Before	After
Chiniofon	117	96	20	1	10.2	1.7	55.5	20.5	47 0	42.7	22.2	3.4	29.1	51.3
Diodoquin	57	56	1	0	15.8	0.0	52.6	3.5	24.6	33.3	8.8	0.0	35.1	66.7
Milibis	138	74	9	55	34.1	0.0	55.1	7.2	46.0	12.3	16.7	0.0	28.2	83.3
Thioarsenites	29	26	3	0	34.5	0.0	72.4	0.0	41.4	0.0	13.8	0.0	24.1	100.0

Distribution of Positive Findings in the Stool Series. The distribution of positive findings in the pre- and post-treatment series of three stool examinations is shown in Table III. E. histolytica was found only in the first post-treatment specimens two weeks after treatment was completed. More than half of the E. coli and other amebas found in the post-treatment series were detected in the first stool. The additional cases found in the second and third stools were proportionately no greater than those of the pretreatment series. Likewise, the frequency with which positives were found in one, two or all of the three stools is essentially the same in the two series.

TABLE III

DISTRIBUTION OF POSITIVE CASES AMONG PRE- AND POST-TREATMENT SERIES OF STOOL EXAMINATIONS

Series	No. of Cases	Species of Ameba	No. of New Cases Found by 1st, 2nd or 3rd Stool			No. Positive in 1, 2 or 3 Stools			Total Positives
			1st	2nd	3rd	1	2	3	
Pretreatment	56	Endamoeba histolytica	9	19	3	12	16	3	31
		Endamoeba coli	25	10	2	8	12	17	37
		Endolimax nana	21	19	2	20	13	9	42
		Iodamoeba butschlii	7	6	2	10	5	--	15
Total untreated			61	55	9	50	46	29	125
Chiniofon	117	Endamoeba histolytica	2	--	--	2	--	--	2
		Endamoeba coli	18	3	3	8	6	10	24
		Endolimax nana	36	9	5	18	19	13	50
		Iodamoeba bütschlii	3	--	1	2	2	--	4
Diodoquin	57	Endamoeba coli	1	1	--	1	--	1	2
		Endolimax nana	7	8	4	9	3	7	19
Milibis	138	Endamoeba coli	7	3	--	4	6	--	10
		Endolimax nana	9	5	4	6	12	--	18
Thioarsenites	29	All negative	--	--	--	--	--	--	--
Total treated	341		83	29	17	50	48	31	129

Housed in dormitory G 3 with the patients treated with thioarsenites were twelve patients of the diodoquin series. Like the thioarsenites group, eight of the diodoquin group were negative for all amebas on three post-treatment stool examinations. The other four were positive

for E. nana, one on the second, two on the third and one on the second and third examinations.

Reactions. Untoward reactions to the various drugs were uncommon. On the third day of treatment two instances of nausea and vomiting occurred among patients taking milibis. Several other patients complained of abdominal cramps, dizziness and headache, some or all of which complaints may have been unrelated to the treatment.

With chiniofon, twenty instances of diarrhea were reported in 176 persons treated. The onset of diarrhea usually occurred on the fourth day of treatment. On the sixth day of treatment one patient had edema of the face and eyelids. The skin on the face appeared thick and red. The temperature was 100°F. orally. The condition disappeared three days after the discontinuance of the chiniofon.

Treatment with diodoquin was discontinued in one patient on the fourteenth day of treatment because of severe constipation and in another because of a severe generalized eruption. The eruption disappeared four days after the drug was discontinued. However, the same eruption appeared twice subsequently when diodoquin was not being given.

In the group treated with thioarsenites one patient complained of severe abdominal pain, of diarrhea and of aching and hurting all over. Large erythematous patches developed on the chest and arms. These areas appeared and disappeared at intervals. Slight edema of the eyelids was noted. There was no nausea or vomiting. The symptoms disappeared immediately after the drug was discontinued. In another patient on the eighth day of treatment fecal impaction developed with abdominal distention and fever which was followed with regression on symptomatic treatment. Three other patients taking thioarsenites had slight nausea and vomiting but were continued on the medication.

COMMENTS

The frequency of various parasitic infections in the present group, as detected by the diagnostic methods used, is indicated in Table 1. Attention has already been called to the variability of the findings in the different dormitories and we have suggested that this variability was in part due to segregation of the subjects, the nature of the parasites, as well as to the variation in the number of stool examinations. That E. histolytica was found in only 12 to 20 per cent of those subjected to one stool examination and in almost 50 per cent of those with three such examinations clearly demonstrates the well known importance of repeated examinations for this organism. The unreliability of laboratory diagnosis of amebiasis and the problem of distinguishing between relapse and reinfection of treated individuals, especially the latter, offer real difficulties in drug evaluation experiments. When amebas are discovered in the post-treatment stools of non-hospitalized individuals, there is justifiable doubt about the origin of the infection. Conversely, when amebas are not found in post-treatment stools, confidence in the negative findings may be lacking. It was because of this evident inability to discover all infections that we decided to treat the whole group with the amebacidal drugs regardless of the results of the stool survey. This permitted us not only to treat those with positive stools but also gave us an opportunity to study reactions to the drugs in a large group at the same time. It also gave us the opportunity to note the effect of these drugs on a large number of infections with non-pathogenic amebas.

From the standpoint of elimination of E. histolytica our results were uniformly good with diodoquin, milibis and thioarsenites. Chiniofon appears to have been less effective because not only was E. histolytica found in early post-treatment stools of two individuals but other species of amebas also occurred with greatest frequency in the group treated with chiniofon. Rated with reference to their effects upon the non-pathogenic amebas, the other three drugs listed in order of their amebacidal activity would stand (1) thioarsenites, which eliminated all species of amebas in all persons treated, (2) milibis, which failed in only a few patients with E. coli and E. nana and (3) diodoquin, which likewise failed in a few patients with E. coli and failed entirely with E. nana. It is of interest that the drugs used appear to have acted similarly on the several species of amebas except E. nana. E. histolytica was most susceptible, followed in turn with I. bütschlii and E. coli. E. nana seems to have been unaffected by either chiniofon or diodoquin but was susceptible to both milibis and thioarsenites, especially the latter. I. bütschlii survived in a very small percentage of instances and only in individuals treated with chiniofon.

In general our results are in agreement with

those of Berberian et al.[1] and Anderson et al.[2] who respectively reported a high degree of efficiency for milibis and thioarsenites. In the first study 92.6 per cent of sixty-seven patients were cleared of E. histolytica for a follow-up period averaging 320 days. However, only twenty-eight of these patients were treated with milibis alone (including three who relapsed following chiniofon) and three of them were reported as relapses, giving a calculated cure rate of 89.3 per cent. As in our experience with the non-pathogenic amebas, they found milibis more effective than chiniofon. I. bütschlii, E. nana and E. coli, respectively, were reduced by 90, 41 and 47 per cent after milibis therapy as compared with 29, 12 and 12 per cent after chiniofon. When Anderson et al.[2] introduced thioarsenites to medicine, they suggested a total dose of 3.0 gm. over a ten-day period. Of eighty-two patients (seventy-seven with E. histolytica, three with Dientamoeba fragilis and two with Balantidium coli), they reported seventy-four patients cleared of their parasites. They did not report results on the common non-pathogenic amebas. Our results with the dosage schedule they recommended confirm the efficacy of thioarsenites in chronic E. histolytica infection of the colon and furthermore indicate the efficacy of these agents against other amebas. Using diodoquin, two tablets four times daily for fifteen days, Manson-Bahr and Muggleton[4] found the drug valueless for dysenteric patients but very effective in curing infections in which only cysts, including those of the non-pathogenic amebas, were being passed. It was implied by these authors that since E. histolytica in the "carrier state" and the non-pathogenic species respond similarly to the diodoquin treatment, E. histolytica may be a non-pathogenic inhabitant of the bowel lumen of those individuals in whom cures are effected by diodoquin.

It is doubtful whether any special significance can at present be attached to any of the aforementioned findings with reference to the non-pathogenic amebas. As compared with the other drugs the greater activity of milibis and thioarsenites against the non-pathogenic amebas does not necessarily indicate greater effectiveness against E. histolytica. Similarly the greater susceptibility of I. bütschlii to all drugs that are effective against E. histolytica does not indicate that this ameba is more pathogenic than E. coli or E. nana or that it possesses or lacks pathogenicity at all. Nevertheless, all other considerations being equal, there probably would be a justifiable inclination to choose the drug that most effectively eliminates the non-pathogens along with E. histolytica. From a practical standpoint it is desirable to have no amebas at all in the stools because of the difficulties of laboratory diagnosis.

Because all patients along with all other members of the hospital population were treated simultaneously with one or another of the test drugs, there was presumably no important source of reinfection except in the individuals who failed to obtain cures. However, since E. histolytica was found in two patients on the first post-treatment examination only two weeks after treatment was completed or three weeks after treatment was started on that particular group, it must be recognized that infective cysts possibly still were being picked up from the physical environment previously contaminated. This possibility can be regarded as remote because the milibis- and thioarsenites-treated groups tended to remain negative for the non-pathogenic amebas despite their contacts in the same dormitories with known positives. Furthermore, the general distribution of parasites in the post-treatment series of stools does not give any indication of reinfection rather than failure to cure. There seems to be no good explanation for the survival of amebas, either pathogenic or non-pathogenic, in some individuals while in many others it dies out on the same drug and dosage.

Untoward reactions to chiniofon were of the type usually reported and will not be commented upon further here. The twenty instances of diarrhea in 176 persons treated represents an incidence of 11.4 per cent, a figure somewhat lower than usually expected. The one skin reaction during treatment appeared to be a drug eruption but chiniofon was not repeated to prove a cause and effect relationship.

Diodoquin produced little or no symptoms although it must be remembered that minor symptomatology is difficult to evaluate in a feeble-minded group. One instance of severe constipation was all that was noted.

In the group treated with milibis two instances of nausea and vomiting occurred on the third day and in several patients dizziness, headache and abdominal cramps were noted. In general, untoward symptoms were mild and infrequent. Berberian, Dennis and Pipkin[1] reported no untoward reactions except a tendency

to constipation. However, increased use of milibis possibly may bring to light other types and instances of reactions, for although the drug is but little absorbed, some of it finds its way into the blood stream. Indeed, one of us (W. A. S.) has seen two patients with multiple neuritis following its use.

In view of Anderson's results[2] we anticipated reactions from the thioarsenites. The drug was used in enteric-coated tablets which possibly reduced the side-effects. Anderson and his group found nausea and vomiting in twelve of 100 patients after 200 mg. doses. We used 100 mg. to the dose and found essentially the same ratio of unfavorable reactions. While Anderson found no cutaneous reactions, in one of our patients the dermal reaction described before developed.

SUMMARY

1. In an institution for the feeble-minded 341 individuals were studied in an attempt to determine the relative efficacy of two well known amebacidal drugs, diodoquin and chiniofon, and two newer drugs, milibis and thioarsenites, that had not at that time been given extensive clinical trial.

2. Stool examinations and treatments both were carried out on a mass rather than an individual basis and all members of the hospital community were treated simultaneously.

3. A pretreatment survey based on one to three stool examinations in all individuals revealed E. histolytica in 12 to 49 per cent of the inmates. The average for the five dormitories was 22.6 per cent. Other amebas found were E. coli, 56.3 per cent; E. nana, 42.5 per cent; and I. bütschlii, 17.0 per cent.

4. In commonly recommended doses chiniofon was given to 117, diodoquin to fifty-seven, milibis to 138 and thioarsenites to twenty-nine patients.

5. Three post-treatment stool examinations made two, three and four to five weeks, respectively, after treatment revealed E. histolytica in only two individuals, both of whom had been given chiniofon and both were positive on the first post-treatment examination.

6. Non-pathogenic amebas were not found in post-treatment stools of the group given thioarsenites. After treatment with milibis E. coli and E. nana were sharply reduced and I. bütschlii was absent. After diodoquin E. coli was sharply reduced and I. bütschlii was absent but E. nana was apparently not affected. In the group treated with chiniofon E. coli and I. bütschlii were somewhat reduced but E. nana was unaffected.

7. In general, untoward reactions to the various drugs were uncommon. With chiniofon the usual diarrhea developed but was present in only 11.4 per cent of the patients, a figure somewhat lower than that usually reported. In the two patients in whom symptoms developed during diodoquin therapy, the symptoms were not definitely related to the diodoquin. One allergic skin reaction developed in the group treated with thioarsenites, and the symptoms of nausea and vomiting previously described by Anderson et al. appeared in three patients but were of only minor degree. The difficulty of evaluating side reactions in a group of mentally defective patients is appreciated.

8. The efficiency of milibis and thioarsenites in the patients with E. histolytica was of high degree and our results confirm the efficacy of these agents against other amebas. Results were uniformly good with diodoquin as well but chiniofon appeared to be less effective.

Acknowledgment: We wish to thank Mr. John Blackledge, Director of the Ellisville State School, for the opportunity to study this group of patients and for the provision of the diodoquin and chiniofon used in the study. Special acknowledgement is due Dr. J. P. Fatherree, Medical Director of the South Mississippi Charity Hospital, whose direction of preliminary investigations and interpretation of their results was largely responsible for the present study. We wish also to thank Dr. P. C. Risher, physician in charge, for supervision of the therapy, and Miss Lorice Camp and Miss Sally A. Bush for the nursing supervision. We would like to acknowledge the help of Eli Lilly and Company which provided thioarsenites, and the Medical Research Department of Winthrop Stearns, Inc. which provided a grant-in-aid of technical assistance and the milibis administered.

Addendum: Approximately one year after treatment two stools about one week apart were examined from 149 individuals of dormitories N and G 1. E. histolytica and I. bütschlii were not found but E. coli and E. nana had returned to the original level, being present respectively in 53.0 and 66.4 per cent. Following the mass treatment in April, 1950, all newly admitted inmates and those who were permitted to re-

enter after leave were routinely treated in an effort to keep the group free from E. histolytica infection. To date (April, 1951) apparently the program has been successful. It is of interest that I. bütschlii, which responded to the antiamebic treatments essentially as did E. histolytica, has likewise failed to reestablish itself in the group.

REFERENCES

1. Berberian, D. A., Dennis, E. W. and Pipkin, C. A. The effectiveness of bismuthoxy p-N-glycolylarsanilate (milibis) in the treatment of intestinal amebiasis. *Am. J. Trop. Med.*, 30: 613–623, 1950.
2. Anderson, H. H., Johnstone, H. G., Bostick, W., Pena Chevarria, A. and Parker, H. Thioarsenites in amebiasis. *J. A. M. A.*, 140: 1251, 1949.
3. Brooke, M. M., Goldman, M. and Johnson, S. A. Polyvinyl alcohol fixative as a preservative and adhesive for protozoa in dysenteric stools and other liquid materials, *J. Lab. & Clin. Med.*, 34: 1554–1560, 1949.
4. Manson-Bahr, P. and Muggleton, W. The response of intestinal amebiasis to diodoquin treatment. *J. Trop. Med. & Hyg.*, 51: 23–27, 1948.

Review

Electrokymography*

II. The Great Vessel and Auricular Electrokymograms

SIMON DACK, M.D. *and* DAVID H. PALEY, M.D.
New York, New York

In a previous review[1] we presented an analysis of the ventricular electrokymogram, including the normal variations of the phase of the cardiac cycle and the abnormalities in myocardial disease, particularly infarction. In this presentation we shall complete the discussion of electrokymography and analyze the normal curves obtained from the aorta, pulmonary artery and left and right auricles, and review the changes which occur in valvular heart disease and congenital lesions. We shall also discuss the application of this method to the study of cardiac arrhythmias and of ventricular asynchronism in bundle branch block and Wolff-Parkinson-White syndrome. The previous review[1] should be consulted for a bibliography of earlier work in electrokymography.

Aortic and Pulmonary Artery Curves. The positional movements which introduce so many difficulties in the analysis of the ventricular electrokymogram may not be as pronounced in the curve obtained from the aorta and the pulmonary artery. In general, the latter resembles a volumetric or pressure curve of the great vessels. Although some distortion due to positional movement does occur, particularly in the ascending aorta, it is usually of minor degree and introduces no serious error in the analysis.

Electrokymograms obtained from the ascending aorta or aortic knob and the pulmonary artery or its branches have the same general contour.[2,3] (Fig. 1.) A representative tracing of the aorta can be obtained most simply from the aortic knob. The curve consists of a steep upward limb during initial rapid ventricular ejection, a plateau-like segment during reduced ejection and a gradual descending limb during diastole. A dicrotic notch or incisura followed by a dicrotic wave is usually visible at the onset of the descending limb. This is a more constant and prominent feature in the pulmonary artery kymogram.

The upward ejection limb is preceded by a short shallow serration occurring during the isometric contraction phase. This is a positional movement produced by traction of the contracting ventricles on the great vessels. Most often it is directed downward but it may also be horizontal or directed upward and merge with the ejection limb. The onset of this serration is approximately synchronous with the onset of the first heart sound. Occasionally there may be another small shallow serration preceding and merging with the above described segment. It is generally associated with the P wave of the electrocardiogram and is therefore due to auricular systole. This earlier serration should not be included when measuring the isometric phase of ventricular systole.

The duration of the isometric contraction phase, as was found for the ventricular electrokymogram, ranges between 0.03 and 0.05 second, averaging about 0.04 second. It is somewhat shorter in the pulmonary artery curve, averaging about 0.03 second. Since the delineation of the serration representing isometric contraction is not always clear, its accurate measurement may be difficult and its employment in measuring the duration of this phase is subject to error. We believe therefore that the method which utilizes the initial rapid vibrations of the first heart sound as the onset of this phase (closure of the A-V valves) and the sharp initial upstroke of the aortic curve as its termination (opening of semi-lunar valves) yields more accurate results.

It should be kept in mind, however, that the initial vibrations of the first heart sound are produced by closure of the A-V valves of both

* From the Cardiovascular Research Group and the Cardiographic Laboratory, The Mount Sinai Hospital, New York, N. Y.

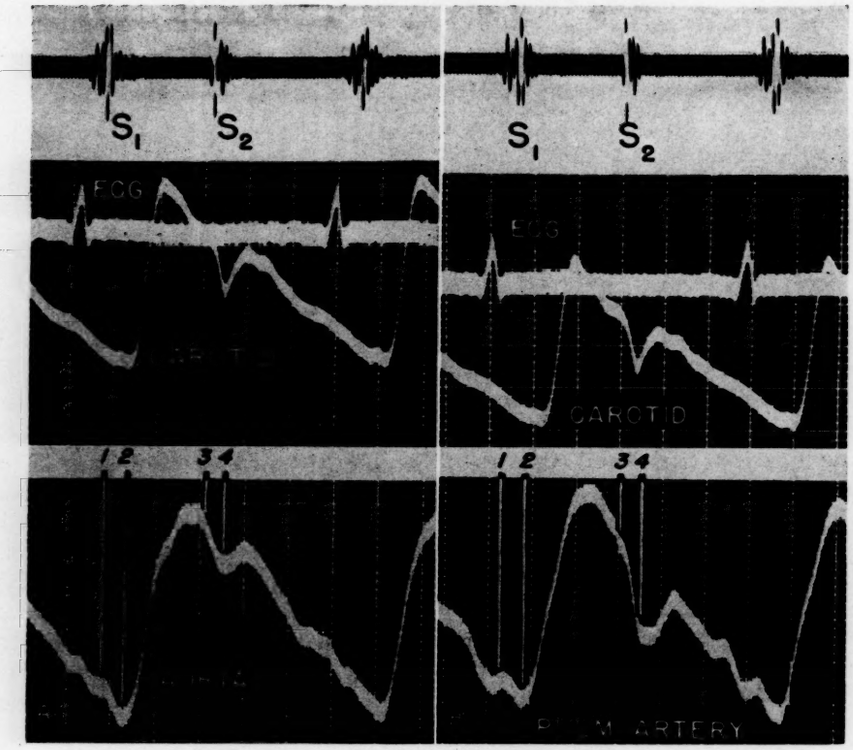


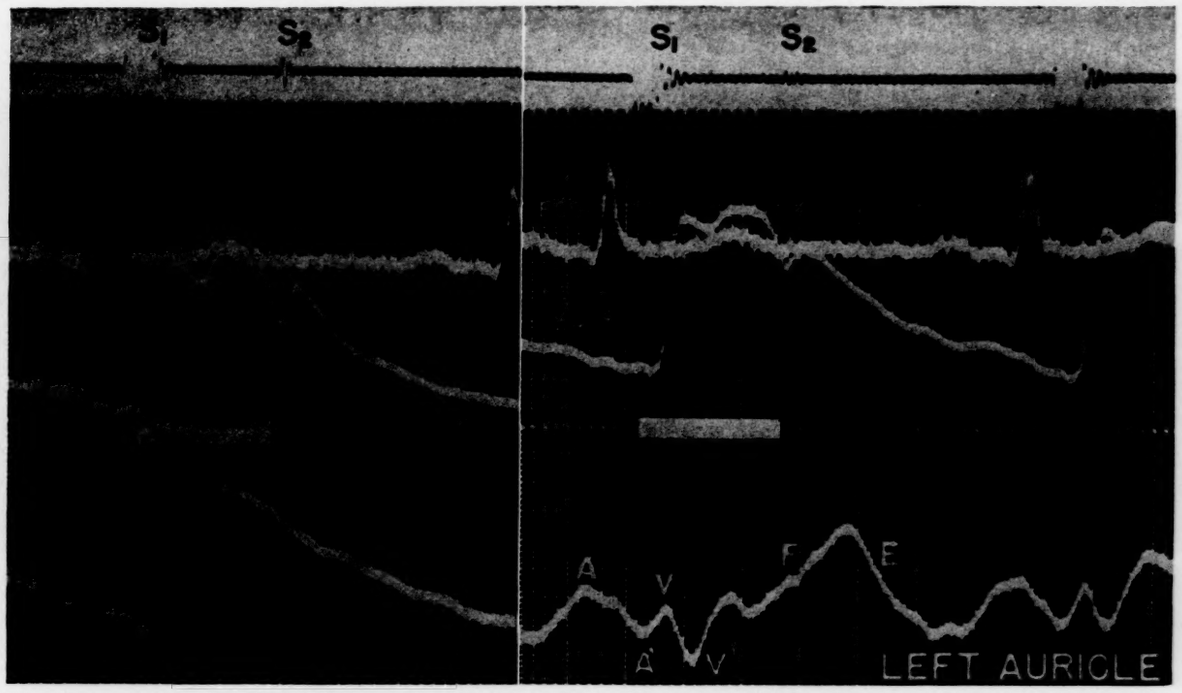
FIG. 1. Electrokymograms of aortic knob (A) and pulmonary artery (B) of normal male adult recorded simultaneously with phonocardiogram, electrocardiogram and carotid pulse tracing. Lines 1-2, isometric contraction phase; 2-3, ejection phase; 3-4, protodiastole. The systolic rise of the pulmonary artery precedes that of the aorta by 0.02 second. The dicrotic notch is more prominent and lower in the pulmonary artery curve. (Vertical time lines = 0.10 second.)

ventricles and similarly the terminal vibrations are caused by closure of the semi-lunar valves of both ventricles. Since a slight asynchronism of left and right ventricular contraction (between 0.01 and 0.03 second) may be physiologic, it is obvious that the initial vibrations are produced by the leading ventricle, which is the right more often than the left. This may introduce a slight error in the calculation of the isometric contraction phase in the aortic as well as in the pulmonary artery curve.

The onset of the ejection phase is delineated by a sharp rise of the aortic or pulmonary artery curve. This is synchronous with the second compound of the first heart sound (semilunar valve opening) and is closely followed by the rise of the carotid pulse. In measuring the latter one must take into account the slight lag in the transmission of the pulse wave to the neck and through the recording system, which may amount to 0.01 to 0.02 second, in addition to the factor of asynchronism between pulmonary artery and aortic ejection. The end of the ejection phase is marked by the onset of the downward limb of the incisura in the great vessel kymogram or carotid pulse curve. It may coincide with the onset of the second sound or precede it by a short interval ranging up to 0.04 second. The duration of the downward limb of the incisura, from onset to nadir, is a measure of the duration of protodiastole, or the time of closure of the semi-lunar valves.[4] This phase generally has a constant duration of 0.04 to 0.06 second. The incisura in the aortic tracing may be very small. (Fig. 2.)

As already stated, the pulmonary artery tracing resembles the aortic tracing but there are minor differences. (Fig. 1.) In the pulmonary artery tracing the peak of the curve is reached somewhat later in systole and is more rounded. The dicrotic notch is usually lower on the descending limb and the succeeding dicrotic wave is more prominent.

Electrokymograms can also be recorded from the hilar branches of the pulmonary artery and even from the peripheral lung fields. These



2 3

FIG. 2. Aortic electrokymogram of normal adult. Note the almost complete absence of the dicrotic notch and wave. (Time lines = 0.02 second.)

FIG. 3. Electrokymogram of left auricular appendage of normal adult. Wave A-A′ represents auricular contraction; A′-V, isometric ventricular contraction (closure of mitral valve); V-V′, ventricular tug on auricle; F, auricular filling during ventricular systole; E, auricular emptying.

may be applied to the study of the pulmonary circulation in congenital heart disease. In the hilar vessel tracings the onset of the systolic rise is slightly delayed as compared to that of the main pulmonary artery; the rise is more gradual and its peak more rounded. The dicrotic wave and incisura are not well defined. The pulmonary parenchymal kymogram is small in normal individuals and requires great amplification for recording. In general, the curve resembles the pulmonary tracing but the onset of the systolic rise is even more delayed than that of the hilar vessel curve. Luisada[5] has shown, however, that the peak of the lung field kymogram is fairly synchronous with that of the hilar vessel tracing, the peak in both tracings occurring slightly after the second sound.

Auricular Curves. The contraction of the left auricle can be studied best in tracings from the middle segment of the left cardiac border in the postero-anterior view. In the great majority of individuals such tracings will show pure auricular curves derived from the left auricular appendage. Auricular tracings can also be obtained from the posterior border in the right and left oblique views. The left auricular kymogram is a much more complex curve than that of the ventricles or great vessels. It is produced by movement of the left auricle not only during auricular systole but also during ventricular systole.

A typical left auricular curve[6] begins with a downward movement which follows the P wave of the electrocardiogram and precedes ventricular systole. (Fig. 3.) This represents inward movement of the auricular wall during auricular contraction. It is followed by a small upward movement at the onset of isometric ventricular contraction (beginning of first heart sound). A second downward movement then occurs synchronous with the systolic rise of the aortic kymogram, which represents a downward tug or traction on the left auricle by the contracting left ventricle and interventricular septum. This also results in drawing down of the A-V septum. The second downward movement occupies the early part of ventricular systole and is succeeded by a gradually rising upward movement during the remainder of ventricular systole. The latter represents auricular filling from the pulmonary

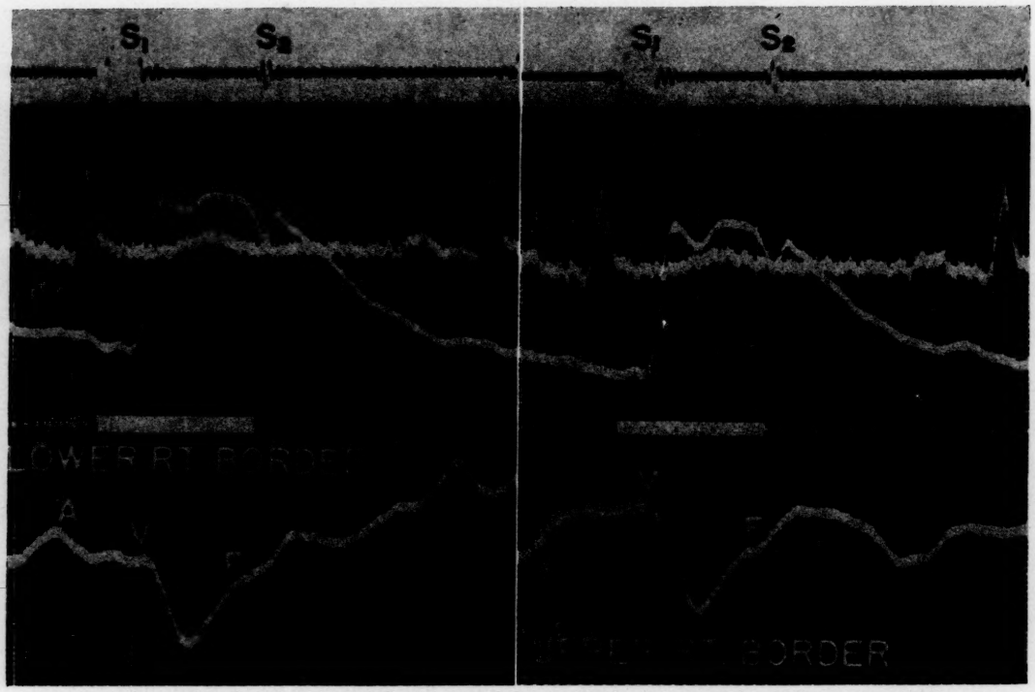


FIG. 4. Normal right auricular electrokymogram. A, curve of lower right border; wave A, auricular contraction; V, ventricular tug; F, auricular filling. B, curve of upper right border. The auricular contraction wave is absent but the ventricular tug (V) is prominent.

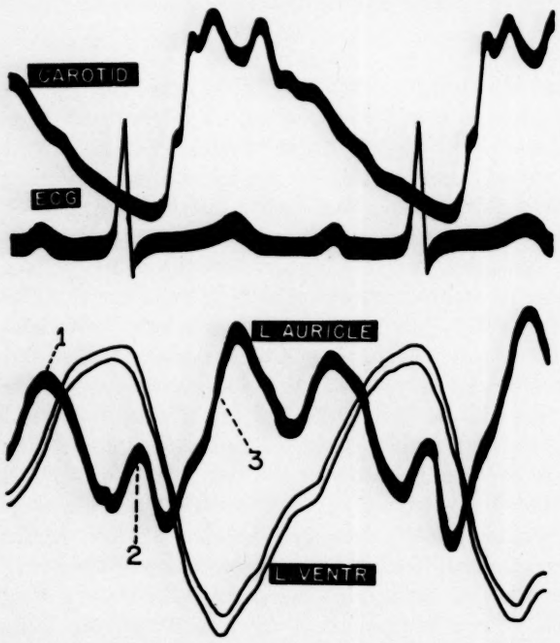


FIG. 5. Superimposed electrokymograms of left auricle (solid line) and left ventricular border (open line) in a patient with aortic stenosis. (See Fig. 11.) Wave 1, auricular contraction preceding ventricular systole; wave 2, ventricular tug due to early ventricular ejection; wave 3, auricular filling during ventricular systole.

veins which causes outward movement of the auricular wall. The contraction of the ventricle, by pulling down the A-V valve and septum, produces a suction effect within the left auricle, resulting in increased inflow from the pulmonary veins and filling of the auricle. The upward movement continues into the isometric phase of diastole. It is terminated by the opening of the A-V valves 0.06 to 0.10 second after the second heart sound when auricular emptying begins. The curve may then show a sharp drop or may continue as a more or less horizontal segment until the next auricular contraction.

The right auricular kymogram is easily obtained by recording from the right cardiac border in the postero-anterior or slight left oblique positions. (Fig. 4A.) The right auricular curve is usually similar to that obtained from the left auricular appendage. Since the right auricle is in close proximity to the underlying right ventricle, the systolic tug produced by the latter is more prominent than that of the left auricular curve and therefore the downward movement at the onset of ventricular systole is usually deeper. As in the case of the left auricle, the latter reaches its nadir in mid-ventricular systole and is succeeded by upward movement representing auricular filling.

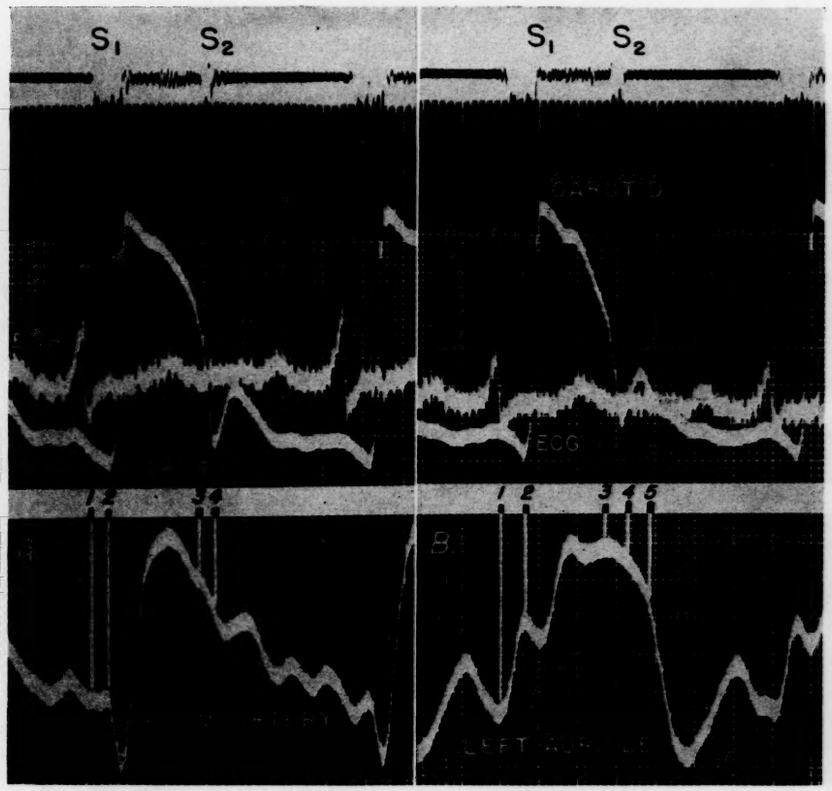


FIG. 6. Rheumatic valvular disease, mitral stenosis and insufficiency. The left auricular curve (B) shows the typical systolic plateau of mitral regurgitation which begins in the isometric ventricular contraction phase (line 1) and is interrupted by a small ventricular tug (line 2). It is sustained until the end of isometric relaxation (line 5). The rise of the atrial plateau precedes that of the pulmonary artery.

It must be borne in mind that both the left and right auricular curves are subject to distortion from transmitted movement of adjacent structures, such as the pulmonary artery and left ventricle on the left side, and right ventricle and ascending aorta on the right side. The atria are thin-walled chambers and are subject to the effects of positional and volumetric changes in the ventricles and great vessels and transmitted vibrations of adjacent structures in addition to the motion produced by their active contraction and relaxation. These factors add to the complexity of the recorded curves and may make accurate analysis difficult.

Considerable variation in the normal auricular kymogram may be observed not only in different individuals but also in different segments of the auricles in the same individual. Not infrequently the auricular ejection movement of the curve is absent and the curve appears ventricular in type. (Fig. 4B.) However, the upward filling movement is seen to begin in mid-systole, indicating auricular rather than ventricular filling. In other patients the auricular ejection movement is the predominant component of the curve and the ventricular tug is small or absent.

Correlation of the auricular and ventricular kymograms can be made by superimposing the two curves or recording them simultaneously.[8] In such a recording (Fig. 5) it will be seen that the first downward wave of the auricular curve (wave 1), representing auricular contraction, occurs in presystole. The second downward wave (wave 2), which is due to the ventricular tug on the auricle, is synchronous with the early ventricular ejection phase. Thereafter, while the ventricular curve continues downward due to continued ventricular contraction the auricular curve (wave 3) now moves upward as auricular filling continues free from the ventricular influence. This upward limb terminates at the end of the isometric relaxation phase of the ventricles. The onset of left and right auricular systolic movement is generally synchronous, although the right auricle may contract 0.02

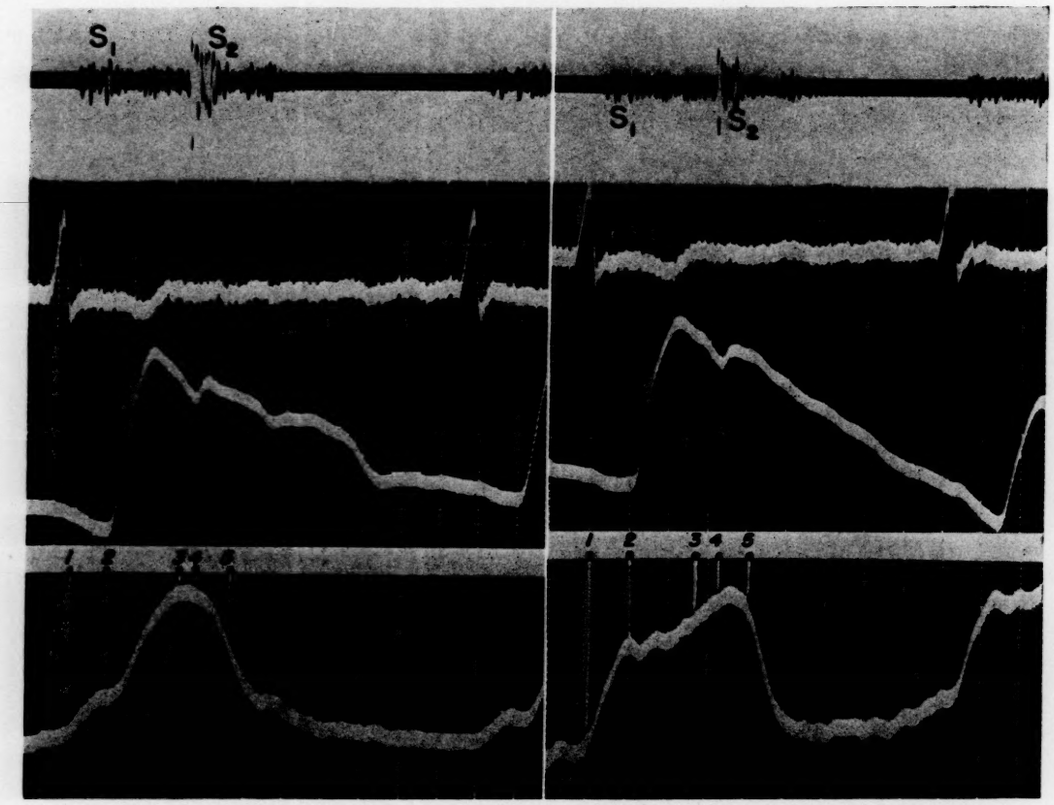


FIG. 7. Rheumatic valvular disease, mitral stenosis and insufficiency, auricular fibrillation. Typical atrial systolic plateau in the left auricular curve (B) indicates mitral regurgitation. The rise of the wave occurs earlier, is steeper and is sustained longer than that of the pulmonary artery curve (A).

second before the left. The onset of the ventricular tug and the end of auricular filling are usually slightly asynchronous in the two auricular curves depending on the degree of asynchronism of the two ventricles.[8,9]

VALVULAR HEART DISEASE

Mitral Insufficiency. In pure mitral insufficiency prolonged regurgitation of blood into the left atrium during left ventricular systole results in increased pressure and blood volume in the left atrium with consequent dilatation and hypertrophy of that chamber. One would therefore expect on physiologic grounds that electrokymographic studies of the left atrium in this condition would reflect these changes in two ways. First, the auricular hypertrophy is manifested by increased magnitude of contraction which is reflected in the electrokymogram as increased depth of the auricular contraction wave. Secondly, the regurgitation would result in varying degrees of sustained outward movement of the left auricular wall during ventricular systole. This phenomenon has indeed been observed by numerous investigators.[10–15]

The systolic plateau has been considered to be pathognomonic of mitral insufficiency by Luisada and Fleischner.[10] The characteristic pattern (Figs. 6 and 7) shows a rapid rise of the auricular curve at the onset of the isometric phase of ventricular systole. The curve continues into a horizontal segment (plateau) which is sustained until the end of the isometric relaxation phase when it drops sharply to the baseline. In less marked degrees of regurgitation a prominent plateau may not be evident but the downward wave of the ventricular tug may be neutralized. (Fig. 8.) The systolic plateau is found more often in tracings of the left atrium in the right oblique view than in tracings of the left auricular appendage. Administration of barium to outline the esophagus may aid in delineating accurately the left atrium.

Luisada and Fleischner observed the atrial systolic plateau not only in patients with a loud

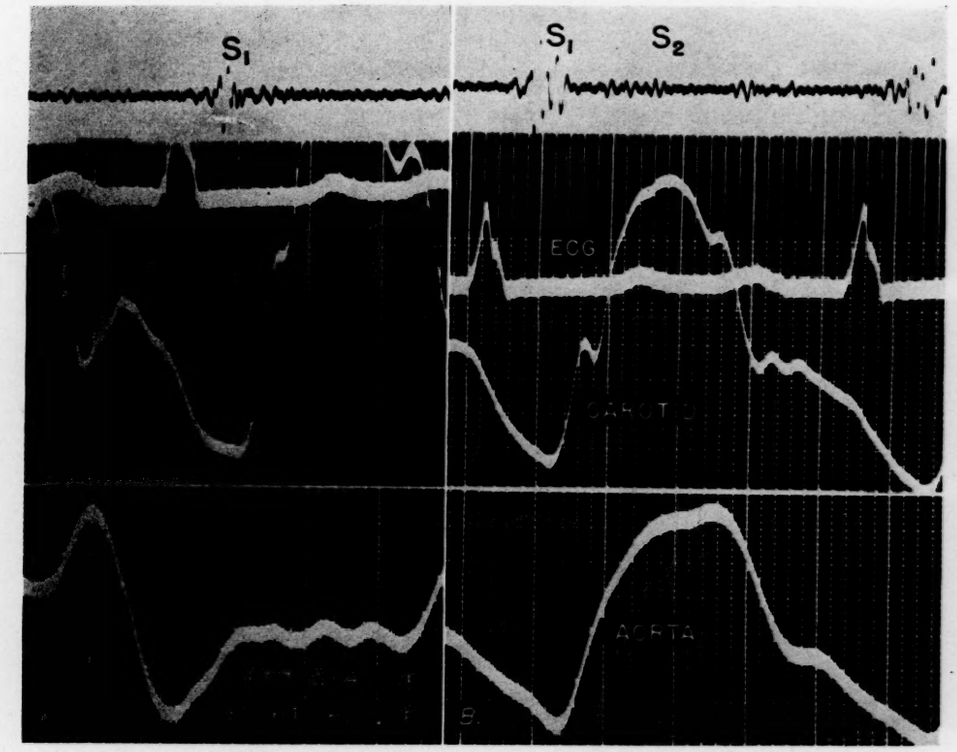
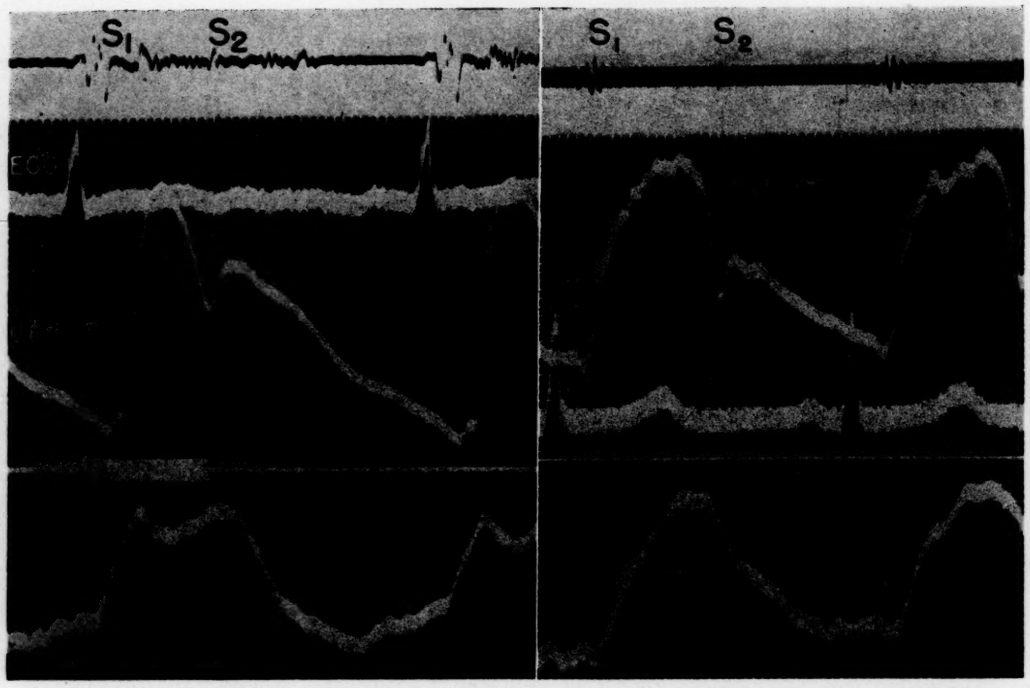


FIG. 8. Rheumatic valvular disease, mitral and aortic stenosis and insufficiency. The left auricular kymogram (A) displays a large auricular contraction wave suggesting left auricular hypertrophy. There is no visible ventricular tug at the onset of ventricular ejection. The aortic curve (B) shows a dicrotic notch and wave low on the downward limb, suggesting aortic insufficiency.

systolic murmur but also in those whom they regarded as "pure mitral stenosis"; i.e., with no murmur indicative of associated mitral insufficiency. Moreover, these authors found the systolic plateau even more marked in auricular fibrillation and believed that it might thus be diagnostic, particularly when no apical murmur could be detected. Lian and his co-workers[13] confirmed these findings. McKinnon and Friedman[15] go even further in their enthusiasm for the systolic outward movement of the left atrium as a diagnostic finding. They believe that an apical systolic murmur may be evaluated by the presence or absence of the atrial systolic plateau and that the murmur is nonorganic if the systolic outward movement of the left atrium is absent.

Criticism of this phenomenon as a diagnostic entity is based largely on the ground that (1) what is considered as purely atrial movement may in reality be that of the closely juxtaposed great vessels or other structures and (2) the altered cardiac dynamics incident to the valvular disease and hypertrophied cardiac chambers may produce positional movements simulating regurgitation. For these reasons considerable caution must be exercised in interpreting the left auricular kymogram in mitral valve disease. The following points may aid in accurately defining the atrial systolic plateau: (1) The pulmonary artery kymogram starts later, usually shows a more gradual rise of the upward limb and may show a dicrotic notch and wave which are certainly not present in the atrial curve. (Figs. 6 and 7.) (2) Hilar vessel tracings are usually even more delayed in their onset and show a much later peak. (3) Densograms of the left atrium, particularly in the right oblique view, will confirm the finding of the systolic plateau when observed in the border tracings. Such a tracing is less likely to be distorted by transmitted movement of adjacent or underlying structures.

From the point of view of typical normal curves obtained over the various chambers it would appear that the systolic atrial plateau is indeed a reflection of mitral insufficiency. However, to disprove that such a curve is not a



9 10

FIG. 9. Rheumatic valvular disease, mitral and tricuspid involvement, auricular fibrillation. The right border electrokymogram shows a typical systolic plateau beginning in the isometric contraction phase, suggesting tricuspid insufficiency.

FIG. 10. Rheumatic aortic stenosis. The aortic curve shows a prominent anacrotic notch (arrow). The carotid pulse tracing also shows an anacrotic notch and superimposed systolic vibrations.

combination of an atrial and arterial curve is not so simple.

We have studied approximately thirty cases of unequivocal rheumatic mitral valve disease. Some had pure mitral insufficiency; the majority combined insufficiency and stenosis. We have found the typical systolic atrial plateau in about 50 per cent of the cases. We have never observed it in individuals with normal hearts. It has been our experience that the characteristic curve was found in moderate to far advanced rheumatic heart disease. Although the presence of this finding strongly suggests the presence of organic mitral regurgitation, its absence in unequivocal cases lessens its value as a diagnostic sign in the questionable case. If it can be definitely established that better technic will demonstrate it in a higher percentage of cases, it may well be one of the best contributions of electrokymography to clinical medicine. Sufficient evidence is not yet available to prove that the phenomenon does not occur in so-called "functional mitral regurgitation" accompanying dilatation of the ventricles in other types of heart disease.

Mitral Stenosis. It is obvious that the electrokymographic findings in mitral valve disease are largely dependent on the degree of involvement of the valves and the disease process in the auricular walls. In a relatively open valve there is likely to be free regurgitation. In the tight fibrotic or calcified valve regurgitation may be minimal or absent. Furthermore, in advanced cases with marked dilatation and thinning and atrophy of the auricular wall the contraction of the atrium may be impaired.

Analysis of our cases has revealed diverse findings so that no characteristic pattern can be predicted. In the average early case, our findings in general are in agreement with those of the other authors[10–15] except that the incidence of systolic plateau observed by us is not as great. In addition to the characteristic systolic atrial plateau in these cases we have also observed increased amplitude of the auricular contraction wave. (Figs. 8 and 25D.) This is the result of the dynamic response of the auricle to the distention of the chamber. In more advanced cases we have observed a variety of findings. Thus the auricular wave may be small or absent in the presence of a systolic plateau. In other cases the auricular contraction wave may be

small and the systolic plateau absent. In auricular fibrillation we, too, have found that the atrial systolic plateau may be more distinct. (Fig. 7.)

It is these diverse findings that have suggested to us that the electrokymogram might prove to be of some value in determining the relative patency of the mitral orifice as an aid in the selection of cases for commissurotomy. Experiments are now under way to determine if such a correlation is feasible. The tight mitral valve, under the stress of increased blood flow incident to exercise or to the administration of certain drugs, cannot deliver the increased volume into the left ventricle, with resultant expansion of the atrial wall. This may be reflected in tremendously increased amplitude of the auricular curve. The relative amplitude of the pulmonary artery and aortic kymogram under these circumstances may yield additional corroborative findings.

Tricuspid Insufficiency. We have observed the typical systolic plateau in curves from the right border of the heart in three cases of tricuspid insufficiency. (Fig. 9.) While in a general way the criticisms leveled against the curves obtained from the left atrium do not apply to those obtained over the right atrium, it is nevertheless worth while to note that the dominating influence of the right ventricle on curves obtained from the right border precludes the possibility of obtaining a pure right atrial curve. The ventricular tug on the right atrium is so great that the resultant downward wave is very deep and it would therefore require a great amount of regurgitation to overcome this wave in order to produce the typical plateau. For this reason we believe that when the typical systolic expansion is noted over the right atrium, this constitutes strong evidence that tricuspid regurgitation is present. On the other hand, cases of milder degree of insufficiency might very well be missed because of failure to overcome the effect of ventricular tug.

In regard to mitral insufficiency it has been considered[15] that the systolic plateau in the left atrium indicated organic valvular disease since it was not found in cases of so-called "functional" mitral insufficiency associated with dilatation of the valve ring. However, this opinion was based on the findings in a very small number of cases and we are not entirely convinced of its validity. In two of our three instances of systolic plateau in the right atrium there was no evidence of rheumatic heart disease or any other condition to suggest organic involvement of the tricuspid valve. (Fig. 14C.) Although these cases did not come to necropsy, on clinical grounds we are almost certain that they represent functional insufficiency secondary to long-standing right ventricular strain. If this is true for tricuspid insufficiency, it is possible that it may also occur in mitral insufficiency.

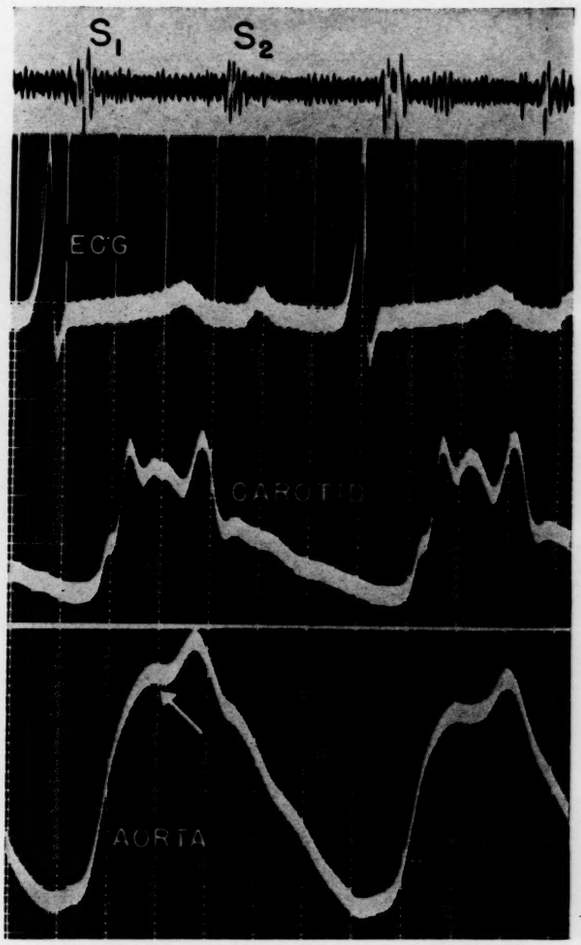


FIG. 11. Rheumatic aortic stenosis and insufficiency. The aortic curve is deformed by a sharp angulation at the junction of the rapid ejection limb and the systolic plateau (arrow), suggesting aortic stenosis. The dicrotic notch is visible and high despite the insufficiency, but there is rapid descent of the early diastolic limb.

Aortic Stenosis. Our findings in pure aortic stenosis are variable. No characteristic pattern of the aortic kymogram has been noted. The most frequent change that we have encountered is a sharply delineated anacrotic notch.[3,16] (Fig. 10.) As already mentioned, the normal aortic kymogram as a rule rarely reveals a

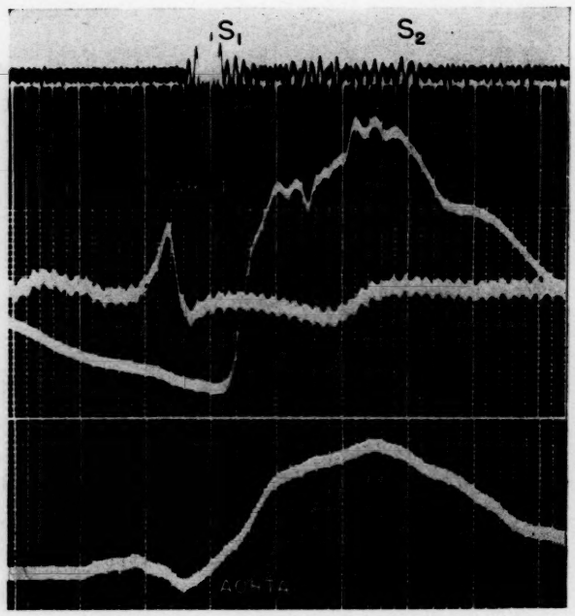


FIG. 12. Rheumatic aortic stenosis. The aortic curve shows a slow rising ejection limb and flattening of the crest. The carotid pulse curve shows typical systolic vibrations.

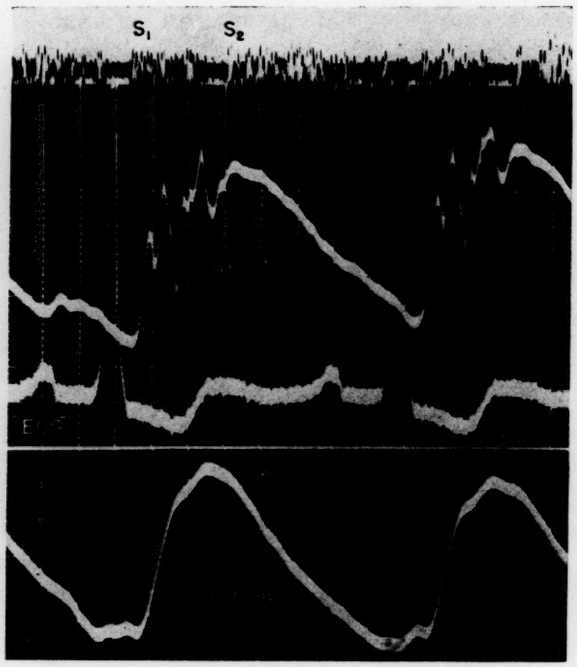


FIG. 13. Rheumatic aortic stenosis and insufficiency. The dicrotic notch and wave are absent in the aortic and carotid tracings probably due to aortic insufficiency. There are typical systolic vibrations in the carotid pulse due to the stenosis, but the systolic rise of the aortic curve shows little deviation from the normal.

clearcut anacrotic notch and, more often than not, there is nothing to suggest it. (Fig. 1.) In several of our cases of aortic stenosis the notch has been so sharp as to produce a sharp angulation of the rising ejection limb, followed by a less steep limb which merges with the rounded crest of the curve. (Fig. 11.) This pattern invariably suggests aortic stenosis but unfortunately it is by no means a constant feature. In fact in some of our cases that have shown the characteristic plateau carotid pulse with classical anacrotic features the aortic kymogram has been disappointingly normal. (Fig. 13.) In other cases the aortic kymogram has shown a slow rise of the systolic limb with rounding of the crest and a semi-sustained horizontal segment which parallels the plateau pulse wave of the carotid artery. (Fig. 12.) But this, too, has been an inconstant finding. In general, we believe that aortic stenosis produces no consistent changes in the aortic kymogram.

Aortic Insufficiency. Characteristic and consistent changes of the aortic kymogram have been reported[16] in this condition. The most notable features described have been (1) a more rapid descent of the early diastolic limb; (Fig. 11); (2) absence or marked diminution of the dicrotic incisura (Fig. 13); (3) the incisura, if present, is situated much lower on the diastolic limb. (Fig. 8B.) While we have been able to confirm all of these findings in some cases, we have not noted them in many other cases of undisputed insufficiency. It has been our experience that the incisura may be small or absent in the aortic kymogram of a large number of normal individuals. (Fig. 2.) This is in sharp contrast to our experience with the normal pulmonary artery curve which almost invariably reveals a well defined dicrotic notch. Under these circumstances absence or diminution of the incisura on the aortic kymogram loses much of its diagnostic significance. The rapid fall of the curve in early diastole is a more constant feature in our cases of aortic insufficiency. But here, too, it is not an invariable feature.

For some reason unknown to us the carotid pulse curve has given a more faithful picture of aortic insufficiency and stenosis than the aortic kymogram.

CONGENITAL HEART DISEASE

Electrokymography is of value in the study of congenital heart disease. Tracings of the pulmonary artery and its hilar branches and of the peripheral lung fields may give information concerning the adequacy of the pulmonary

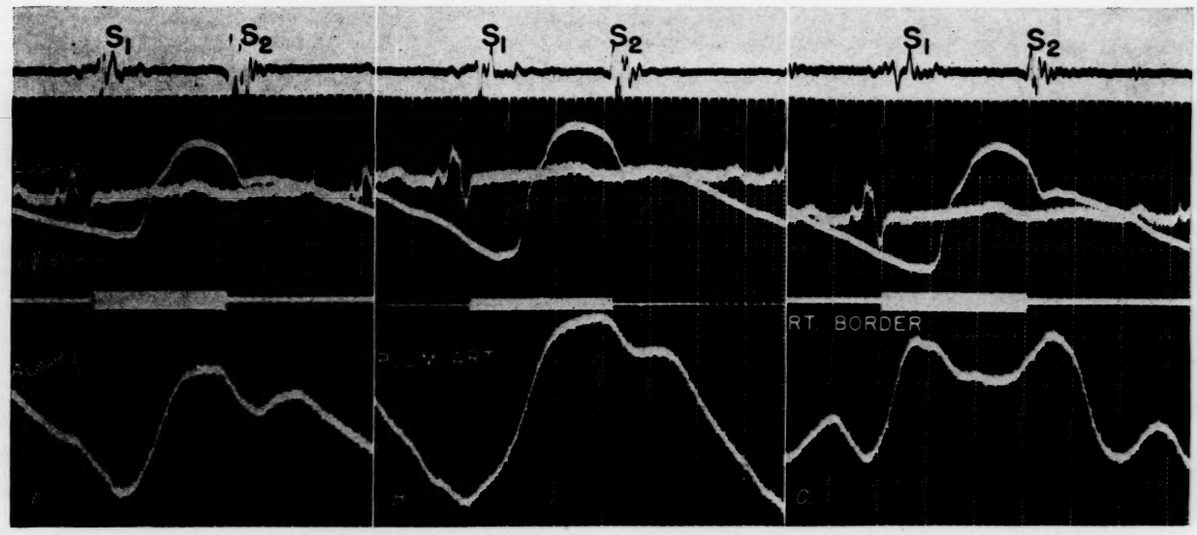


FIG. 14. Congenital heart disease, Eisenmenger's complex. The pulmonary artery curve (B) is very prominent as compared to the aortic curve (A). The right border tracing (C) shows a normal auricular contraction wave but a huge systolic plateau, suggesting functional tricuspid insufficiency.

circulation.[5,17] Tracings from the right cardiac border may help to detect right auricular hypertrophy.[11]

In lesions associated with increased flow and pressure in the pulmonary artery and its branches electrokymograms recorded from these vessels show striking increase in amplitude as compared to the aortic tracing. (Fig. 14.) This becomes more significant when the increased amplitude involves the pulmonary artery branches as well as the main vessel, giving rise to a "hilar dance." (Fig. 15.) This phenomenon is observed most commonly in interatrial septal defect, Lutembacher syndrome, patent ductus arteriosus and conditions associated with functional pulmonic insufficiency. In these conditions the peripheral lung field tracing (Fig. 16), recorded over the lung in the mid-clavicular line at the level of the second or third interspace anteriorly, also shows increased amplitude, indicating increased flow and pulse pressure within the smaller pulmonary arteries and arterioles.*

In congenital lesions which produce diminished pulmonary blood flow and pulse pressure, electrokymograms recorded from the pulmonary artery and its branches are generally small and deformed and the systolic rise is delayed.[5] Tracings from the peripheral lung fields are unobtainable. This occurs in isolated pulmonic stenosis and tetralogy of Fallot. In one case of severe pulmonic stenosis with interatrial septal defect (Fig. 17) it was impossible to record a pulmonary artery kymogram in the postero-anterior view while in the right oblique view the pulmonary artery curve was deformed and showed a delayed rise.

In patent ductus arteriosus the pulmonary artery pulsations are very dynamic and are also of increased amplitude as compared with those of the aorta. The systolic limb rises more rapidly than normal due to increased pulse wave velocity and increased filling from the aorta, and the dicrotic wave following the prominent incisura is higher.

In congenital lesions associated with right-sided hypertrophy and strain electrokymograms recorded from the right cardiac border generally show very deep auricular waves. (Fig. 17.) This is suggestive of right auricular hypertrophy and dilatation. We have observed this particularly in pulmonic stenosis and interatrial septal defect. Not infrequently the increased right atrial contraction is associated with prominent pre-systolic venous and liver pulsations which are confirmatory signs of the increased pressure within the right auricle due to obstruction of right ventricular outflow.[18]

* It must be obvious to the reader that the amplitude changes discussed are purely qualitative in nature and therefore have limited value. The lack of quantitation in the electrokymograph has been one of its greatest disadvantages. Fortunately, this has been apparently overcome with the successful production by Morgan and Sturm (The quantitative electrokymograph. *Circulation*, 4:605, 1951) of an instrument by means of which accurate calibration may now be expected.

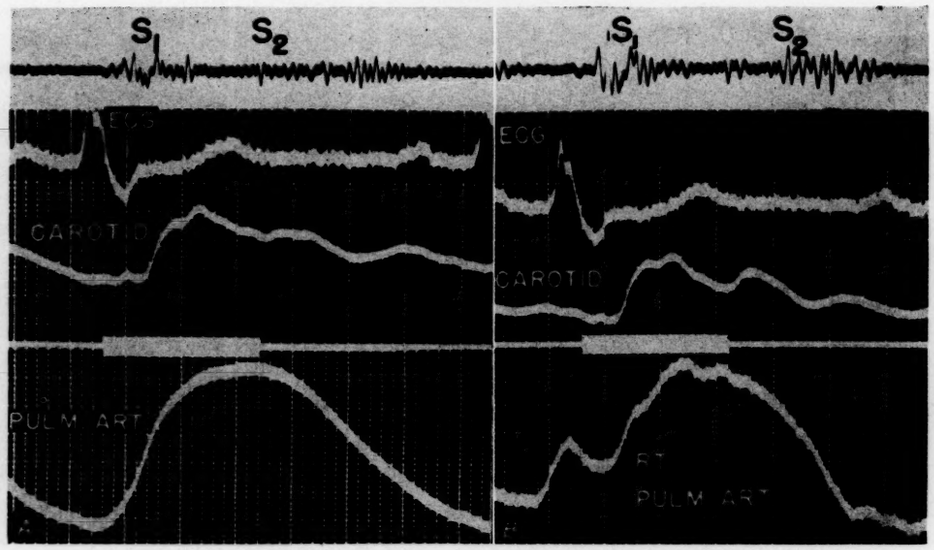


FIG. 15. Congenital heart disease, Lutembacher syndrome. The pulmonary artery curve (A) is prominent and there is no dicrotic notch or wave, as seen in pulmonic insufficiency. The right hilar curve (B) is also prominent, due to hilar dance.

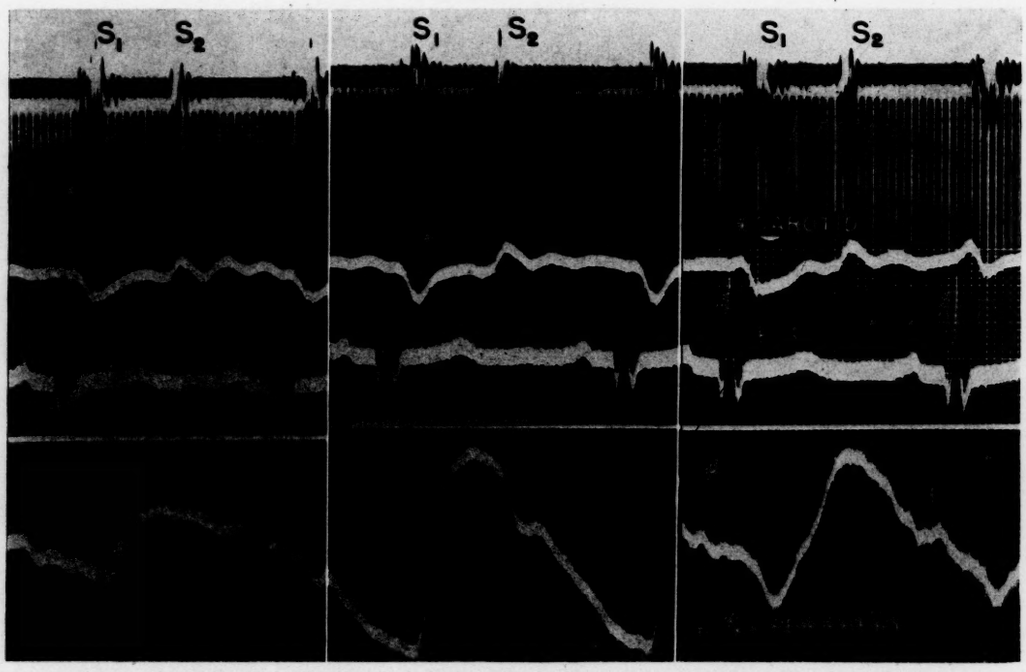


FIG. 16. Congenital interatrial septal defect. The aortic curve (A) is small and deformed. The pulmonary artery curve (B) is normal but prominent. The peripheral lung field tracing (C) is large, suggesting increased pulmonary blood flow. Note the delayed onset of the curve. (Carotid pulse is deformed due to artefact.)

In congenital subaortic stenosis the aortic tracing may show a prominent anacrotic notch, as described in acquired aortic stenosis.

Another congenital lesion well suited for study by electrokymography is aberrant pulmonary vein. When a right pulmonary vein inserts into the right auricle or its tributaries, there is a visible band-like shadow adjacent to the right cardiac border. If a left pulmonary vein inserts into the right auricle or its tributaries, an abnormal shadow may be visible along the upper left cardiac border. Since these abnormal para-

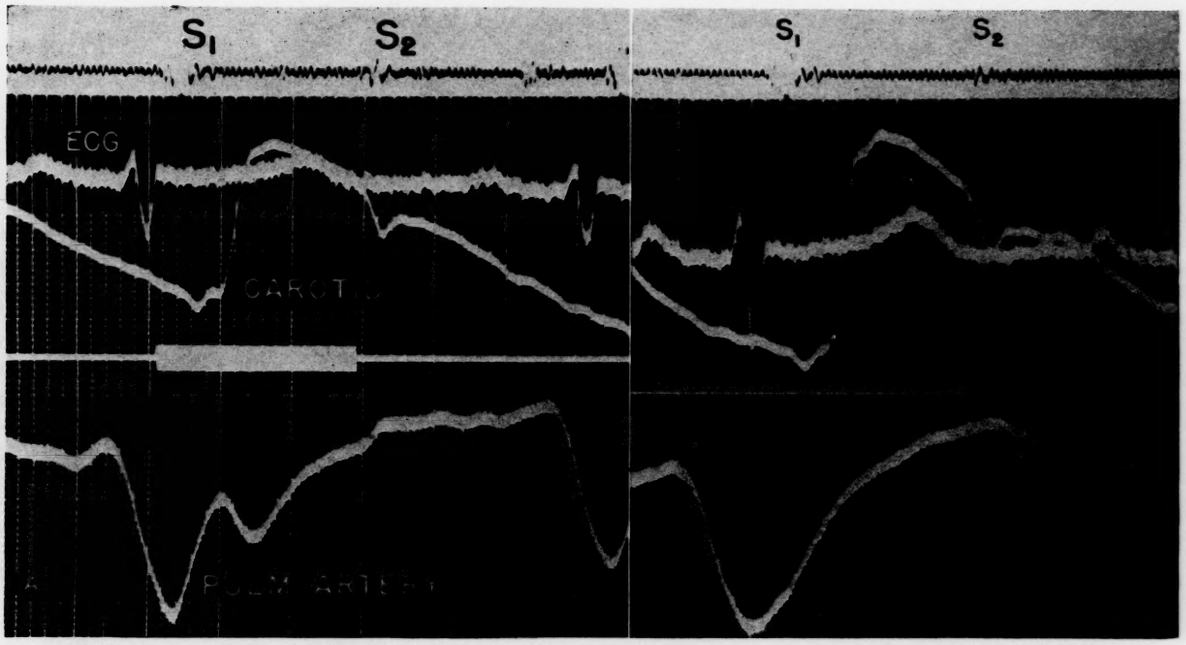


FIG. 17. Congenital pulmonic stenosis with interatrial septal defect. The tracing from the pulmonary artery region (A) shows a large auricular component but no arterial curve. The right border electrokymogram (B) shows a huge auricular contraction wave due to right auricular hypertrophy.

cardiac shadows may pulsate, electrokymography may attain diagnostic value by demonstrating that their recorded movement is venous in type and not arterial, thus distinguishing them from branches of the pulmonary artery or aorta.

In one case of interatrial septal defect associated with aberrant left pulmonary vein angiocardiography demonstrated that the latter emptied into the left innominate vein. The aberrant vein was visible along the upper left mediastinum and pulsated actively when observed fluoroscopically.[19] A similar pulsating paramediastinal shadow on the right side was shown to be a dilated superior vena cava. Electrokymograms of the two paramediastinal structures showed a venous type of movement (Fig. 18) in contrast with the normal arterial curves obtained from the left pulmonary artery and aorta. The recorded tracing of the aberrant pulmonary vein showed significant differences from the tracings of the superior vena cava and right and left auricles.

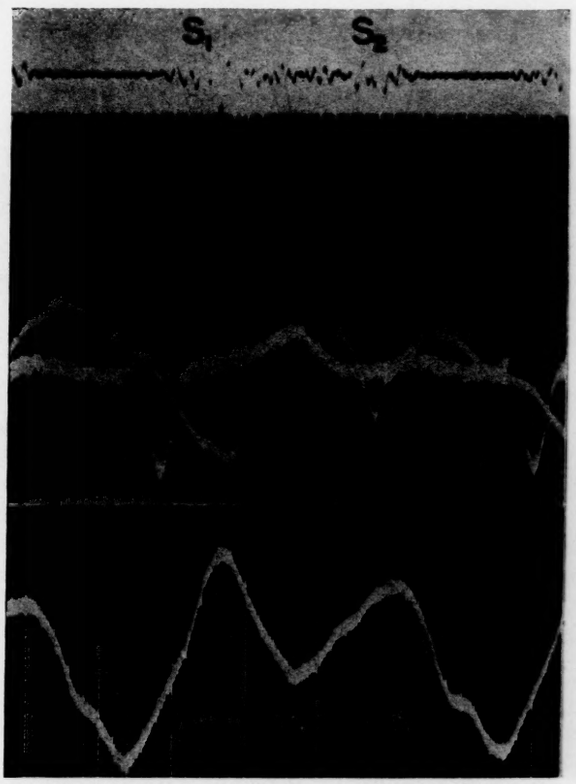


FIG. 18. Aberrant pulmonary vein inserting into left innominate vein. The electrokymogram shows a venous or auricular type of curve. There is a prominent downward limb during diastole and presystole and a smaller downward limb at the onset of ventricular ejection.

VASCULAR ANEURYSM VS. MEDIASTINAL OR LUNG TUMOR

Differentiation of aortic and pulmonary artery aneurysm from mediastinal tumor is often difficult. The reason for this is that a nonvascular mass situated in close proximity to

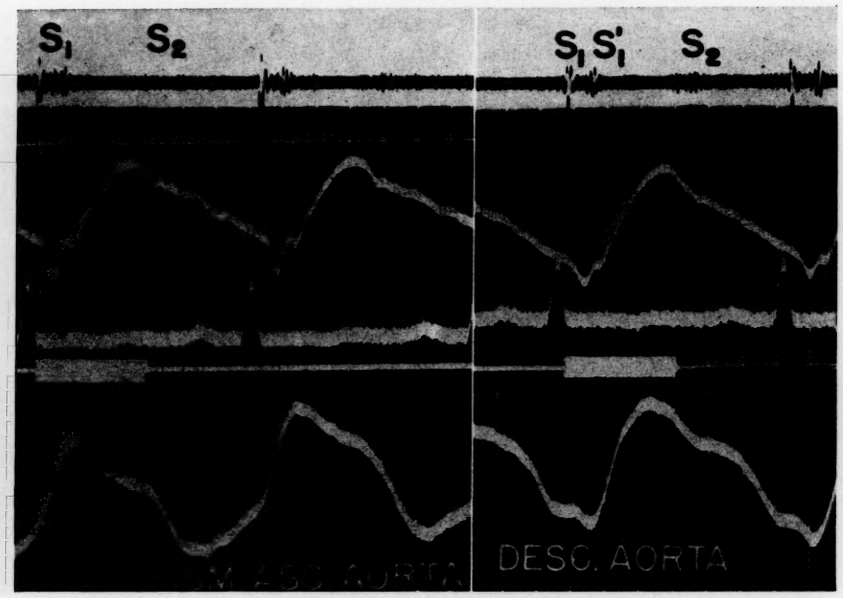


FIG. 19. Aneurysm of ascending aorta. The electrokymogram of the aneurysm (A) shows a rapid steep rise at the onset of ventricular systole and a rapid fall at the onset of diastole. The curve of the descending aorta (B) is normal.

the thoracic aorta, pulmonary artery or hilar vessels may appear to pulsate actively because of transmitted pulsations and thus simulate an aneurysm of the great vessels or their branches. On the other hand, a true arterial aneurysm may show very little active pulsation because of an intravascular clot and may thus simulate a tumor mass. Roentgenkymography[20] is of value in the differential diagnosis but electrokymography is superior in this respect because of greater sensitivity, amplification and ease of exploration.

The diagnosis of an arterial aneurysm kymographically rests on the demonstration of expansile arterial pulsation rather than transmitted movement. An expansile pulsation produces outward and inward movement of the border of the mass in all directions. In other words, the systolic ejection movement of the electrokymogram will be directed in opposite directions on the upper as compared to the lower border of the aneurysm and on the right as compared to the left border. In a transmitted pulsation the movement is in the same phase on all borders. If the mass is sufficiently large to allow the recording of a densogram over the center of the mass, an arterial type of tracing is observed similar to those obtained from the border of the mass.

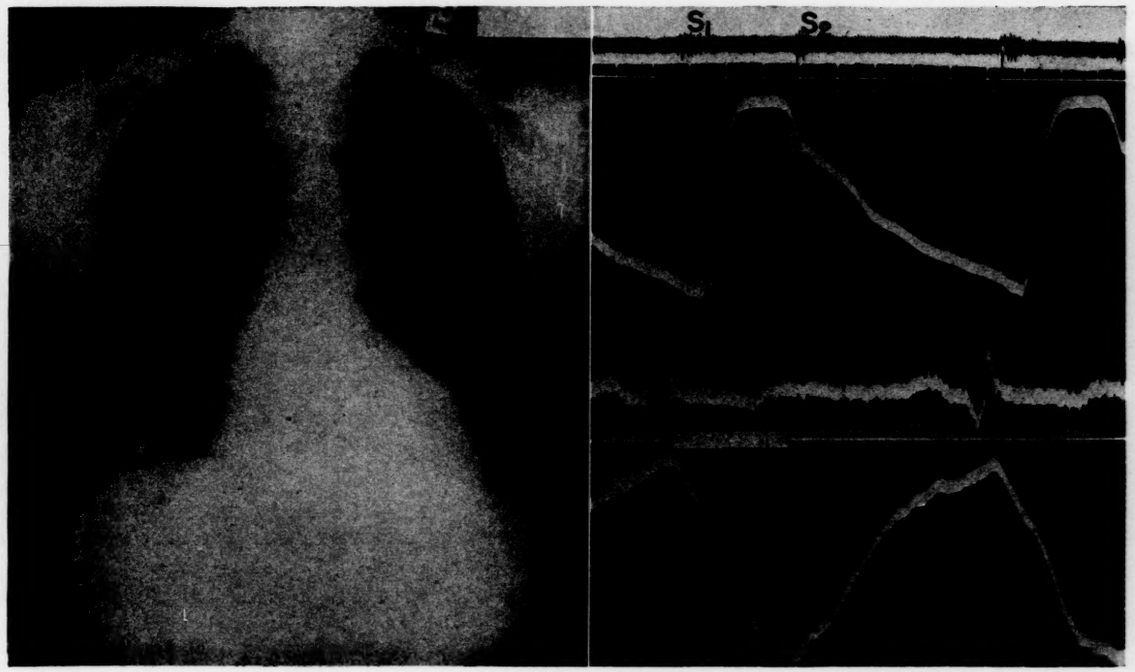
When such expansile arterial pulsation is demonstrated a positive diagnosis of aneurysm can be made. It must be remembered, however, that the absence of expansile movement does not entirely exclude an aneurysm since the presence of a laminated clot within it may abolish active arterial pulsation.

In several cases of aortic aneurysm we have noted a characteristic distortion of the kymographic tracing recorded over the aneurysm when compared with the tracing obtained from the other segments of the aorta. (Fig. 19.) The systolic ejection phase over the aneurysm was noted to rise more rapidly and to reach its peak earlier in the cycle. The collapse of the curve at the onset of diastole was also more abrupt than in the remainder of the aorta. This suggests a ballooning-out of the aneurysm in early systole and rapid collapse of its walls in early diastole.

In occasional instances of lung or mediastinal tumor situated in close proximity to the left ventricular border the powerful ventricular movements may be transmitted to the mass and differentiation from ventricular aneurysm may be difficult. Kymographic border tracings and densograms (Fig. 20) may aid in the diagnosis.

VENTRICULAR ASYNCHRONISM

Electrokymograms of the aorta and pulmonary artery have been applied to the study of the relation of electrical and mechanical systole



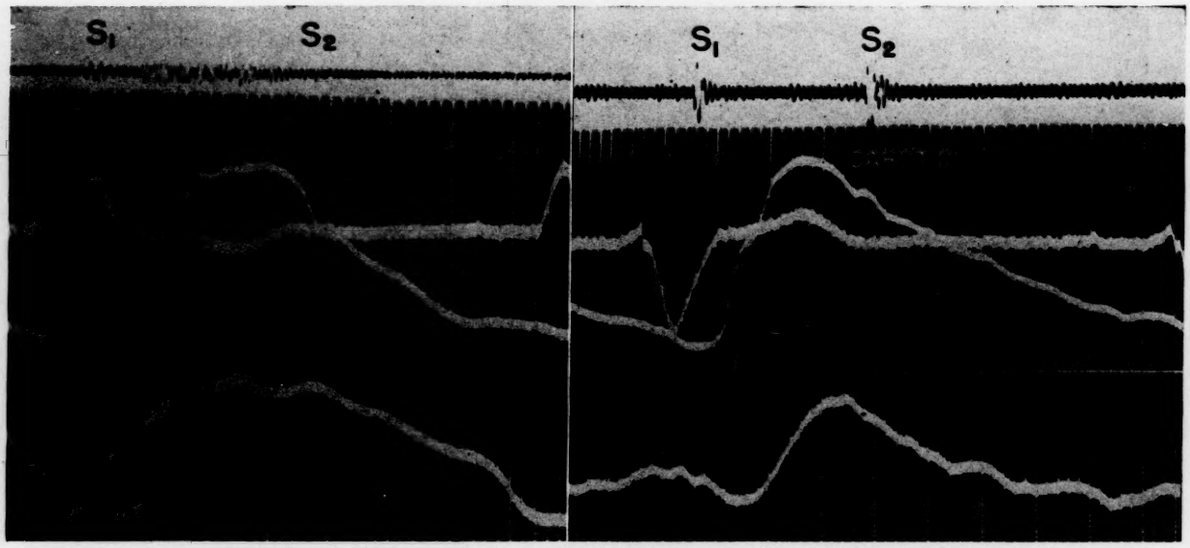
20A 20B

FIG. 20. A, Lipoma of the left lobe adjacent to the left ventricle, simulating ventricular aneurysm on teleoroentgenogram and fluoroscopy. The electrocardiogram (lead III) shows typical findings of old posterior wall infarction. B, the kymogram from the border of the tumor and left ventricle is normal, excluding ventricular aneurysm.

of the ventricles.[21] The left and right ventricular electrokymograms are not as accurate for this purpose, for not only may they be distorted by positional changes of the heart borders but the onset of the ejection phase in the latter is not as sharp as the systolic rise of the great vessel curves. The time of onset of left ventricular as compared with right ventricular ejection can be determined by comparing the aortic-carotid and pulmonary artery-carotid time intervals, respectively.

Analysis of the great vessel electrokymograms of a large number of normal individuals has indicated that slight asynchronism of left and right ventricular ejection is a normal physiologic phenomenon.[21–23] Normally there may be a lag between the onset of pulmonary artery and aortic ejection ranging between +0.03 and −0.02 second. (Fig. 1.) That is, pulmonary artery ejection may precede aortic ejection by 0.01 to 0.03 second or follow it by 0.01 to 0.02 second. In all these measurements one must take into account the differences in time of transmission of the pulse wave from the left and right ventricles to the great vessels, especially if the aortic knob is employed to record the aortic curve.

The early reports on the findings in bundle branch block seemed to indicate that there existed a significant degree of asynchronism of left and right ventricular ejection in this condition, depending on the side of the electrical conduction defect. In sixteen cases studied by Ellinger and his co-workers[21] left bundle branch block was usually associated with delay in left ventricular ejection (pulmonary artery-carotid time increased to 0.04 to 0.07 second) and right bundle branch block with delay in right ventricular ejection (carotid-pulmonary artery time increased to 0.03 to 0.07 second). In a more recent study, however, based on simultaneous recordings of pulmonary artery and ascending aortic electrokymograms and electrocardiograms Samet and his co-workers[23] cast doubt on the validity of these findings. In complete left bundle branch block there was a significant lag between pulmonary and ascending aortic ejection in only twelve of twenty-three cases. In complete right bundle branch block there was a significant delay in pulmonary artery as compared with aortic ejection in only eleven of thirty-eight cases. These authors stressed the observation that irrespective of the presence or absence of mechanical asynchronism in bundle branch block, mechanical ejection was delayed in both ventricles as shown by the



21 22

FIG. 21. Left bundle branch block. The pulmonary artery curve begins 0.05 second before the carotid tracing, indicating delay in left ventricular ejection.

FIG. 22. Right bundle branch block. The pulmonary artery curve begins 0.06 second after the carotid tracing, indicating delay in right ventricular ejection.

prolonged interval between onset of QRS and pulmonary artery and aortic ejection.

Our own limited observations seem to confirm the presence of significant mechanical asynchronism in the majority of cases of bundle branch block. We have studied fourteen cases of bundle branch block, six of the left type and eight of the right type. These were cases in which the presence of bundle branch block was proved by intracardiac and esophageal electrocardiography and by vectorcardiography, for it is well known that right and left ventricular hypertrophy can produce conventional electrocardiographic patterns almost identical with those of right and left bundle branch block, respectively.

In the six cases of complete left bundle branch block pulmonary artery ejection preceded carotid artery ejection by 0.04 second in one case, 0.05 second in two cases and 0.06 second in three cases, indicating a significant delay in left ventricular ejection in all. (Fig. 21.) In the eight cases of complete right bundle branch block pulmonary artery ejection followed the rise of the carotid curve by 0.01 second in one case, 0.02 second in one case, 0.04 second in three cases, 0.05 second in two cases and 0.06 second in one case, indicating a significant delay in right ventricular ejection in six cases. (Fig. 22.)

In one of the patients with left bundle branch block the block was intermittent and could be produced by any procedure which increased the heart rate such as exercise and inhalation of amyl nitrite. This case afforded an opportunity to compare the pulmonary artery to carotid time in successive cardiac cycles as the QRS duration increased from 0.08 to 0.12 second. (Fig. 23.) It was noted that during normal intraventricular conduction the onset of pulmonary artery ejection preceded the rise of the carotid artery by 0.03 second, which is within the range of normal. Several cycles later, when the QRS interval increased to 0.11 second, the pulmonary artery preceded the carotid artery by 0.06 second, indicating a delay of 0.03 second in right ventricular ejection during the bundle branch block as compared to the normal state for this patient. When the QRS duration reverted to normal, there was a corresponding shortening of the pulmonary artery-carotid time.

Recently it has been suggested[26] that the curves obtained from the ascending aorta and even from the aortic knob may be subject to greater positional changes than those obtained from the pulmonary artery and this may alter significantly the take-off of the aortic curve. Thus comparison of the aortic and pulmonary artery curves to detect ventricular asynchronism may lead to error. For this reason Chamberlain and his associates[26] have discarded the aortic

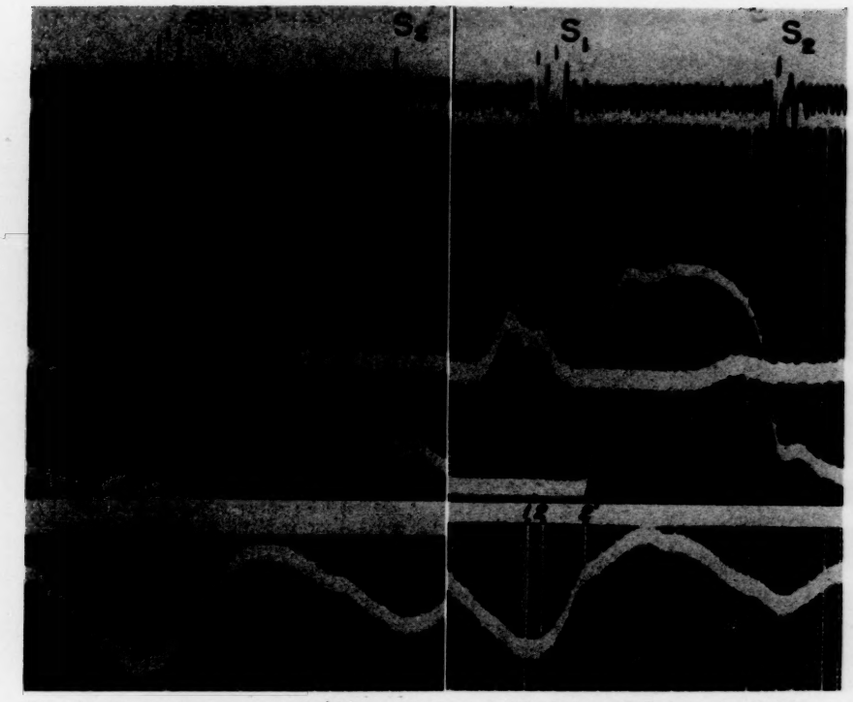


FIG. 23. Intermittent partial left bundle branch block. A, QRS duration 0.08 second. Pulmonary artery-carotid time (lines 2-2′) measures 0.03 second which is normal. B, five cycles later; QRS duration 0.11 second. Pulmonary artery-carotid time (lines 2-2′) increased to 0.06 second, indicating delay in left ventricular ejection.

curve for this purpose and depend only on the lag between pulmonary artery and carotid pulse. The measurements in our small group of cases were obtained by the latter method. On the other hand, Phillips[27] applied this method in twenty-two cases of right bundle branch block and found evidence of mechanical asynchronism in only six cases.

The question of the presence or absence of mechanical asynchronism in bundle branch block apparently cannot be settled conclusively by electrokymography at the present time. This is due to several distorting factors inherent in the method such as positional changes of the great vessels and cardiac borders which affect the systolic take-off of the curves, and physiologic variations in the time of onset of the carotid pulse curve. Bearing these facts in mind, the preponderance of evidence suggests nevertheless that mechanical asynchronism exists in the majority of cases of proven bundle branch block.

Observations in Wolff-Parkinson-White syndrome,[22,28,29] however, have shown consistently that there may be no mechanical ventricular asynchronism, although there is electrical pre-excitation of the left or right ventricles through anomalous auriculo-ventricular pathways. The absence of asynchronous ventricular contraction has been attributed to (1) a slower rate of propagation of the aberrant impulse which offsets the premature excitation of the affected ventricle; (2) the terminus of the aberrant pathway may be near the interventricular septum and the impulse spreads simultaneously through both ventricular walls; and (3) premature excitation may occur in both ventricles by way of functioning aberrant pathways in both ventricles and exclusion of the His-Purkinje system.[30]

CARDIAC ARRHYTHMIAS

Electrokymographic analysis in the various cardiac arrhythmias often leads to interesting observations concerning the mechanical behavior of the cardiac chambers and great vessels. This applies particularly to premature beats, paroxysmal tachycardia, auricular fibrillation and flutter and A-V heart block. Correlation of the electrokymogram with the other reference tracings yields physiologic data concerning the inter-relation of auricular and ventricular con-

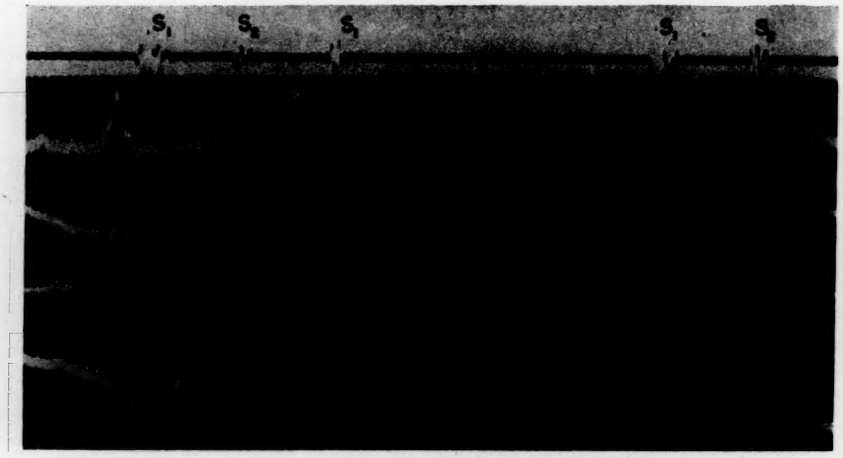


FIG. 24. Ventricular premature beat (arrow). Note almost absent pulmonary artery and carotid ejection and absent second heart sound. First heart sound is slightly diminished. The succeeding beat following the pause shows increased carotid and pulmonary artery ejection curves. The first heart sound is slightly increased.

traction, the effect of heart rate on the latter, and the factors responsible for variation in ventricular contraction and intensity of the heart sounds. In selected cases of complex or undiagnosed arrhythmias the electrokymogram

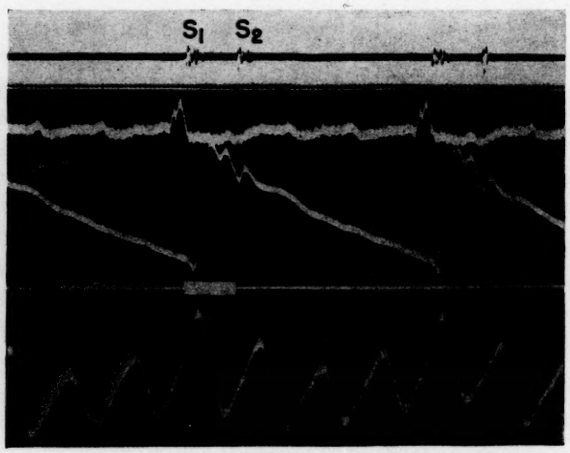


FIG. 25A. Rheumatic mitral valve disease, 4:1 auricular flutter. Electrokymogram of left auricular appendage shows rapid regular auricular contractions associated with each flutter wave in the electrocardiogram. Every fourth flutter wave occurring simultaneously with the ventricular contraction becomes taller during the isometric contraction phase.

may be of diagnostic aid by demonstrating the presence or absence of auricular contraction and the time of its occurrence in the cardiac cycle.

Premature Beats. In general, a premature beat is characterized by smaller amplitude of the ejection limb in the ventricular, aortic and pulmonary artery kymograms. (Fig. 24.) Due to the smaller ejection the carotid pulse tracing is usually small. If the beat is very premature, it may be represented merely by a shallow notch on the descending limb of the aortic, pulmonary artery and carotid tracings. The first heart sound may be accentuated, normal or diminished but the second sound is generally very small or even absent, owing to the small aortic ejection and the weaker snap during closure of the semi-lunar valves.

Not only is the amplitude of the ejection phase smaller in the premature contraction but the rate of descent of the ventricular curve and ascent of the great vessel curves are more gradual. Also, the time of onset of the ejection limb in these tracings as well as in the carotid pulse tracing is often significantly delayed. For this reason the attempt[23] to use premature beats to study ventricular asynchronism is prone to great error, and the electrocardiogram is much more reliable in determining the origin of the premature beat.

In the cycle which follows the pause after the premature beat the amplitude of the ejection limb is strikingly increased in the ventricular and great vessel kymograms and the first sound may be louder. (Fig. 24.) The increased amplitude of ejection is directly related to the increased ventricular filling during the compensatory pause, producing a greater ventricular contraction and ejection.

Auricular Flutter. Tracings of the left auricular appendage and right border in auricular flutter generally show rapid regular auricular move-

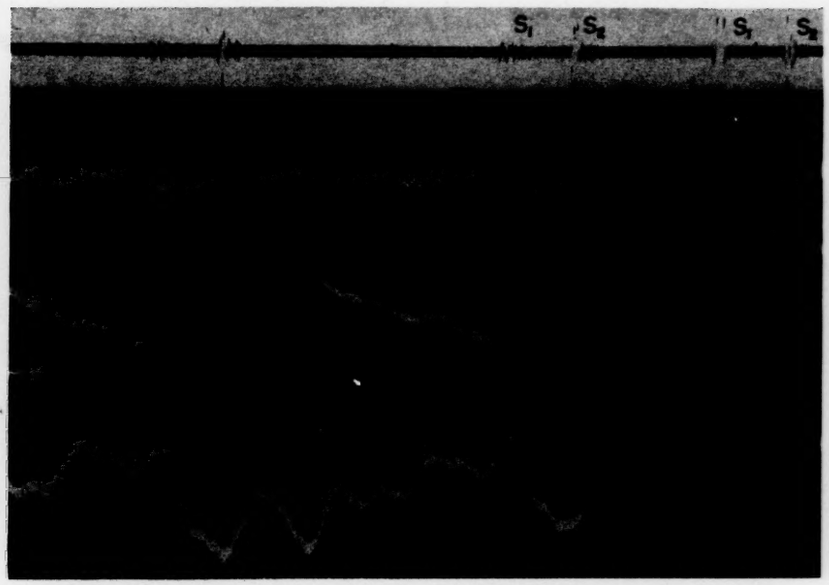


FIG. 25B. Same patient with alternating 4:1 and 2:1 auricular flutter; electrokymogram of the right border. The right auricular flutter waves are smaller and show distortion due to right ventricular influence. Note accentuated first heart sound in third ventricular cycle (arrow) when the P-R interval is 0.14 second.

ments corresponding to the flutter waves in the electrocardiogram. (Fig. 25A.) Each auricular movement consists of a sharp downward contractile limb and a less steep upward expansile limb. The auricular movements are generally uniform in amplitude and configuration except during cycles where there is a simultaneous ventricular contraction. In these cycles the upward limb of the auricular wave is increased in height. This occurs during the isometric phase of ventricular contraction which produces backthrust of the A-V valve into the auricular cavity. The downward wave is deeper owing to the additional factor of ventricular tug on the auricle.

The right auricular movements in auricular flutter are generally smaller than those recorded over the left auricular appendage, particularly in the presence of mitral valve disease. (Fig. 25B.) Also, the movements of the right auricle are not as symmetrical and show greater distortion from the superimposed right ventricular contraction.

The electrokymogram of the aorta and pulmonary artery in auricular flutter often shows superimposed upward movements of the descending limb. These bear a definite relation to the flutter waves in the electrocardiogram and represent transmitted auricular movements. They are similar to the transmitted auricular movements we have observed in heart block.[31] Similar upward movements may also be superimposed on the kymographic tracings obtained from the upper and mid-left ventricular border which may simulate abnormal ventricular contraction due to myocardial disease. (Fig. 25C.)

It is well known[32] that in auricular flutter the first heart sound may vary in intensity in different cycles. This is dependent on the length of the P-R interval, that is, on the relation of auricular to ventricular systole. For example, in one of our cases in which there was alternating 4:1 and 2:1 flutter (Fig. 25B) it was observed that when a flutter wave began 0.12 second before the QRS the amplitude of the first heart sound was increased threefold as compared to the cycle in which the P-R interval was only 0.06 second. Nevertheless, despite the accentuation of the first sound in the former cycle the amplitude of the ventricular, aortic and carotid tracings was distinctly decreased. The decreased amplitude of ventricular ejection was related to a shorter diastolic interval and therefore decreased ventricular filling. This apparent paradox of loud first sound with decreased or normal ventricular contraction and ejection also has been observed in extrasystoles and complete heart block[31] and strongly suggests that the intensity of the first sound is governed by the position of the A-V valve leaflets at the onset of ventricular contraction rather than the force of ventricular contraction

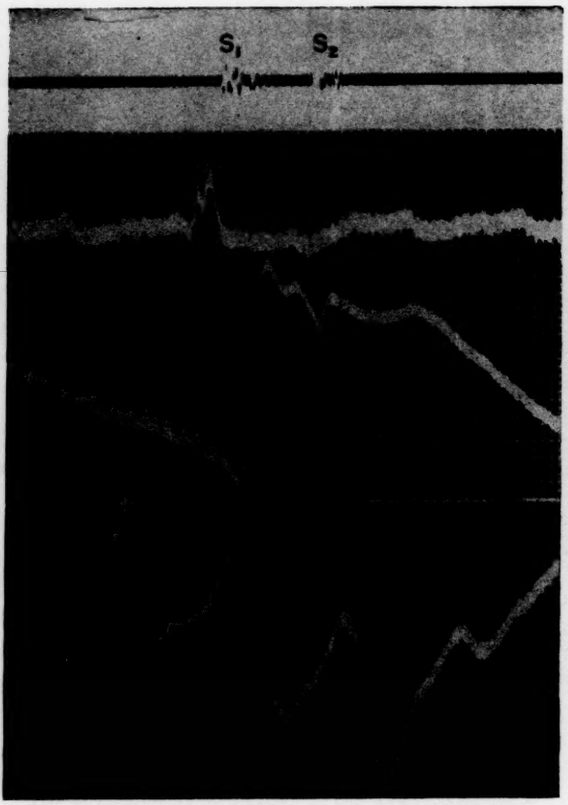


FIG. 25C. Auricular flutter, same patient. Electrokymogram of upper left ventricle distorted by superimposed auricular flutter movements which are particularly prominent during ventricular systole. The abnormal curve should not be attributed to myocardial disease.

alone. This will be discussed further in the section on heart block.

Auricular Fibrillation. In auricular fibrillation electrokymograms of the left auricular appendage and right cardiac border do not show coordinate auricular contractions. Auricular tracings show no downward movement in presystole.[11] (Fig. 7.) Small fibrillatory movements may also be visible in the tracings of both auricles.

The electrokymogram has been of aid in differentiating auricular flutter from auricular fibrillation. In several patients with a grossly irregular and rapid rate in whom the electrocardiograms seemed to show typical auricular fibrillation in all leads without any evidence of flutter waves, the electrokymogram of the left and right auricles revealed rapid, regular uniform auricular contractions due to auricular flutter. In one case these flutter movements, at a rate of 430 per minute, were also superimposed on the pulmonary artery tracing.

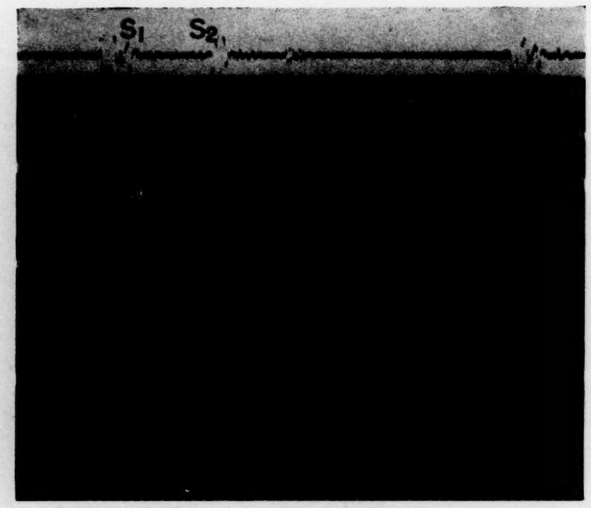


FIG. 25D. Same patient following restoration of normal sinus rhythm; electrokymogram of left auricle. Note the large auricular contraction wave due to left auricular hypertrophy and the neutralization of the ventricular tug at the onset of systole suggesting mitral insufficiency.

Auricular fibrillation affords a good opportunity to study the effect of the length of the diastolic interval on volume changes in the ventricles and great vessels and on the intensity of the first heart sound.[33] This study has yielded several interesting physiologic observations which are detailed in another publication.[34] (Fig. 26.)

Heart Block. Electrokymography in patients with complete A-V heart block affords an opportunity to study the auricular contractions undistorted by ventricular movement and to determine the effect of auricular contraction on the first heart sound and ventricular filling.[31] Analysis of the records of ten cases of complete A-V block has yielded the following data:

Electrokymograms of the right cardiac border and left auricular appendage region consist of pure auricular movements dissociated from the movement of the ventricles. (Fig. 27A.) Auricular systole in all cases is represented by a downward movement beginning approximately 0.10 second after the onset of the P wave. The auricular wave reaches its greatest depth 0.10 to 0.14 second after its onset and then returns to its precontraction level. The onset of left and right auricular contraction is fairly synchronous but in several cases right auricular contraction preceded left by 0.2 second.

The amplitude of the auricular waves was influenced by their proximity to ventricular systole. In some of the cases there was a striking variation in the amplitude of the auricular con-

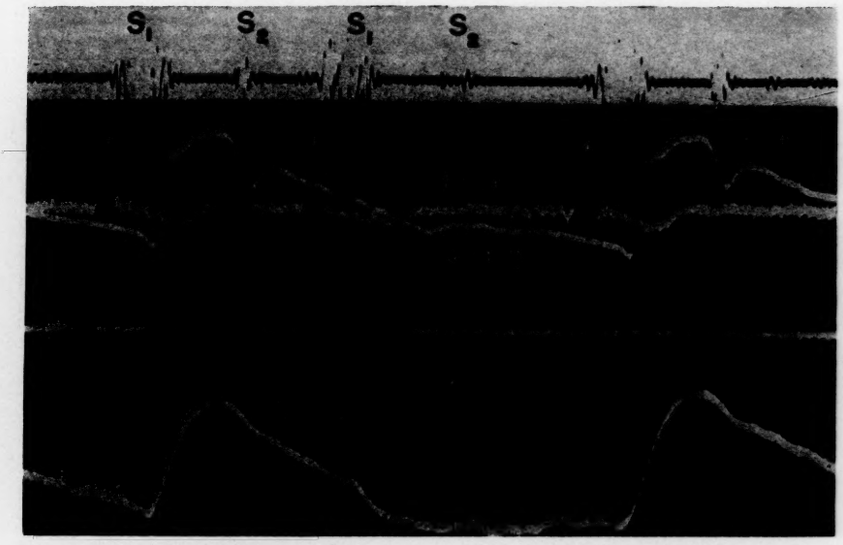


FIG. 26. Aortic electrokymogram in auricular fibrillation. The second ventricular beat follows a short diastolic interval and is associated with almost absent aortic and carotid ejection waves, diminished second heart sound but a perfectly normal first heart sound. The third cycle follows a longer diastolic interval. Note the prominent aortic and carotid curves, a normal second heart sound, but an unchanged first heart sound.

tractions as their position changed in relation to ventricular systole. In general, it was noted that the largest auricular waves occurred during ventricular systole and the smallest during late ventricular diastole when the P wave and auricular wave just preceded the QRS or ventricular contraction. Venous pulse tracings in these cases showed a similar variation in the height of the "a" wave which coincided with the amplitude of the auricular contraction. It should be emphasized, however, that in other cases the amplitude of the auricular wave was fairly constant, irrespective of their position in the cardiac cycle.

The above observation would seem to indicate a direct relationship between the amplitude of auricular contraction and the phase of ventricular activity in which it occurs. The largest auricular contraction occurs during ventricular systole when the ventricles are under high tension and the A-V valves are closed, and the smallest auricular contraction occurs in the latter part of ventricular diastole when the A-V valves are open and the ventricles are filled. A large auricular contraction is also observed when it occurs during isometric relaxation of the ventricles before the A-V valves have opened.

Another factor influencing the amplitude of auricular contraction, in addition to the open or closed state of the A-V valves, is the degree of auricular filling. It has been demonstrated[35,36] that auricular filling is aided by ventricular systole which is accompanied by pulling down of the A-V septa and valves, producing a suction effect within the auricles and increased inflow from the great veins. An auricular contraction occurring in early ventricular diastole thus produces a movement of large amplitude owing to the greater auricular filling which has occurred during the ventricular systole immediately preceding it. An auricular contraction in late diastole produces a smaller movement because optimal auricular filling has not occurred in this phase owing to the continual flow of blood through the open A-V valve.

Of greater physiologic interest are the observations concerning the variation in intensity of the first sound in complete heart block and the relation of this phenomenon to the proximity of auricular to ventricular contraction. These observations may throw light on the mechanism of production of the first heart sound. Auscultation and phonocardiography in complete heart block have repeatedly demonstrated the occurrence of "bruit de canon" or periodic accentuation of the first heart sound.[31,37] Simultaneous electrocardiograms indicate that the accentuated first sound occurs when the P-R interval is short and auricular contraction precedes

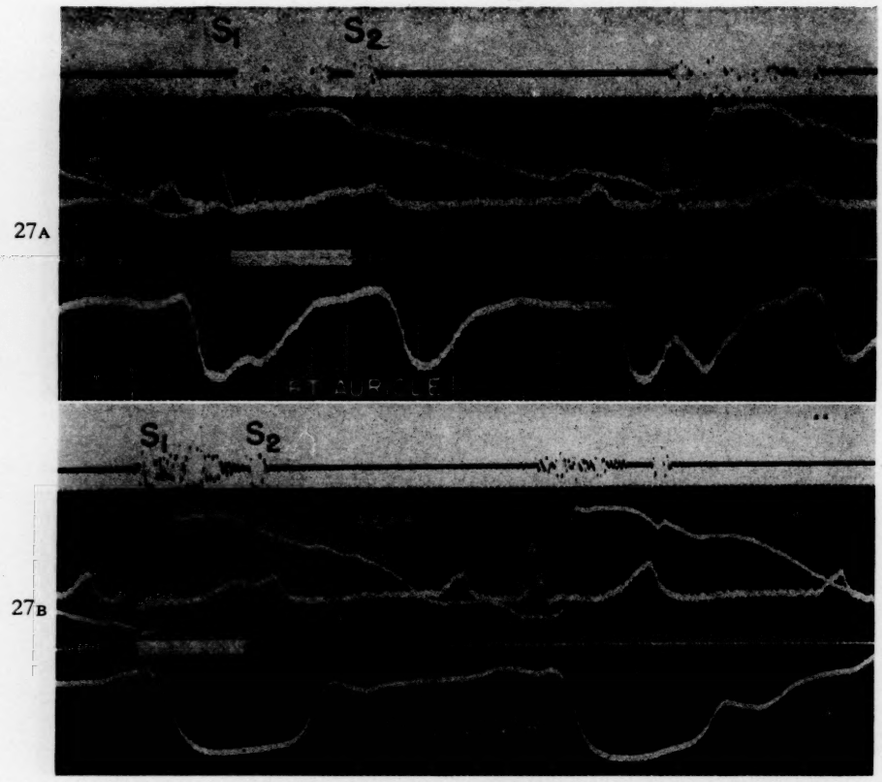


FIG. 27. A, Complete A-V heart block. Electrokymogram of right border showing regular auricular contraction waves. In this case they do not vary in amplitude as their position in the cardiac cycle changes. Note the small ventricular tug superimposed on the first and third auricular waves. B, Complete A-V block, same patient. Comparison of the left ventricular electrokymogram with the other reference tracings shows that the louder first sound in the first cycle is not accompanied by increased amplitude of the ventricular or carotid curves. However, the P-R interval is shorter in the first cycle (0.17 second) than in the second cycle (0.27 second).

ventricular contraction by 0.06 to 0.12 second. The simultaneous tracings obtained in our cases confirm these previous observations. It was noted that the first sound was accentuated consistently whenever the P-R interval fell between 0.04 and 0.14 second. When the P-R interval was longer than 0.18 second, the first sound became faint. The electrokymographic tracings of the ventricles and great vessels revealed that an accentuated first sound was not accompanied by increased amplitude of the ventricular, aortic or pulmonary artery pulsations. (Fig. 27B.) In other words, despite the marked variation in the intensity of the first sound the electrokymograms remained unchanged. This excludes increased ventricular filling or increased force of ventricular contraction as the primary cause for the loud first sound.

The correlation of the accentuated first sound with a short interval between auricular and ventricular systole rather than with increased ventricular ejection points to the A-V valves as the major factor in the production of the loud first sound. Two opposing explanations for the latter have been presented, both based on the short interval between auricular and ventricular systole. Wiggers[4] and Wolferth and Margolies[38] attributed the loud first sound to the building up of greater initial ventricular tension and therefore a stronger ventricular contraction which occurs when ventricular systole closely follows auricular systole and the A-V valves are in optimal position for closing. On the other hand, Dock[39,40] believed that sudden tensing of the A-V valve leaflets produced the major vibrations of the first sound and that the intensity of the sound was related to the tension of the valve leaflets at the onset of ventricular contraction. Soon after auricular

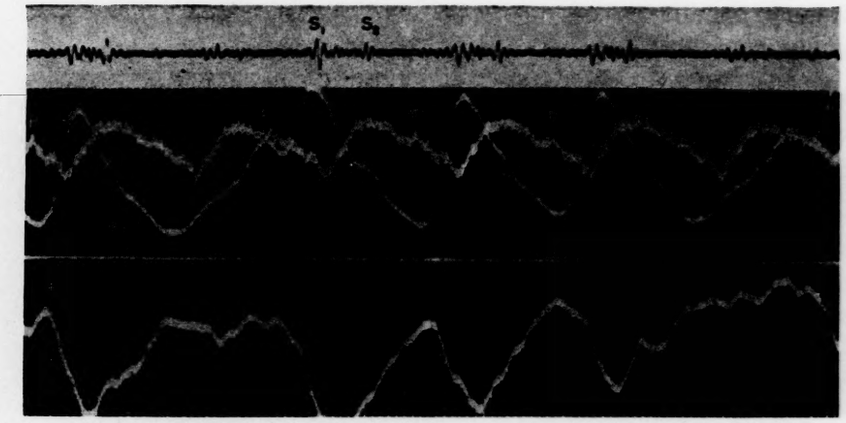


FIG. 28. Ventricular tachycardia with retrograde conduction to the auricles and periodic block of the retrograde impulse, resulting in frequent dropping of the retrograde P wave. During the latter cycles the electrokymogram of the right cardiac border shows no auricular contraction wave, and in the jugular pulse there is no "a" wave. Note the variation in intensity of the first heart sound as the position of the auricular contraction with relation to the succeeding ventricular systole changes from cycle to cycle.

contraction the A-V valve leaflets are slack and pressed toward the ventricle by the high intra-auricular pressure. Ventricular systole occurring at this time will produce a loud first sound when the slack is suddenly taken out of the valve leaflets.

Paroxysmal Tachycardia. The opportunity for recording electrokymograms in paroxysmal tachycardia does not arise often owing to the short duration of most episodes and to the disability associated with their occurrence. Occasionally, however, such an opportunity does arise and the tracing may be of diagnostic aid in determining the abnormal cardiac mechanism underlying the tachycardia. Thus in a case of ventricular tachycardia of long-standing which responded poorly to treatment the correct interpretation of the complicated arrhythmia was made from analysis of the electrokymogram of the right cardiac border recorded simultaneously with the usual reference tracings.[41] (Fig. 28.)

This analysis indicated that there was a paroxysmal ventricular tachycardia with retrograde conduction of the ectopic impulse to the auricles, producing a P wave following each QRS. Due to A-V block there was progressive delay in retrograde conduction which periodically produced complete block of the retrograde impulse and dropping out of the P wave. This was manifested in the right auricular kymogram by periodic disappearance of the auricular contraction wave and in the venous pulse by disappearance of the "a" wave. The ventricular kymogram showed a persistently regular rhythm at the time the auricular contraction was blocked out.

In regard to the previous discussion concerning the variation in the intensity of the first heart sound in auricular flutter and heart block, it is of interest to note that in this case the first sound became faint in the cycles in which the auricular contraction failed to occur. The loudest first sound was noted when retrograde ventricular-auricular conduction was delayed and auricular systole preceded the succeeding ventricular systole by a short interval. This re-emphasizes the influence of the auricular contraction and the state of the A-V valves on the intensity of the first sound. Also it may account in part for the varying intensity of the first sound in most cases of ventricular tachycardia.

SUMMARY

In these reviews we have attempted to provide a broad and comprehensive picture of the electrokymographic method as applied to normal and abnormal cardiac states. In the previous article[1] we discussed the ventricular border curves. In the present review we have dealt with the movements of the atria and great vessels. We have recorded our own findings and as far as possible have tried to present the views of other workers in the field. The nature of the articles has precluded detailed discussion, which the interested reader will find in papers on specific subjects. At all times we have been

careful to point out the limitations of the method and the possibilities for error in interpretation.

Over three years of experience has convinced us that study of the mechanical behavior of the cardiac chambers and of the great vessels is of great physiologic interest and may be diagnostic in certain cardiac aberrations. It should be emphasized that many of the recorded findings had already been noted with the roentgenkymograph. However, we believe that the electrokymograph is a greatly superior instrument, chiefly because of its greater sensitivity, ease of exploration of the entire cardiac silhouette and the availability of other graphic methods simultaneously recorded for correlation and analysis. Such simultaneous recordings have been fruitful in the delineation and study of the phases of the cardiac cycle, particularly the isometric periods, despite certain discussed hazards of measurement. The influence of auricular and ventricular contraction on the production of the heart sounds is clearly discernible by this method. Also, the occurrence of ventricular asynchronism may be detected.

In our hands, the greatest clinical value of the instrument has been attained in the study of diseases of the myocardium and, more specifically, of myocardial infarction. This has been discussed fully in the previous review.[1]

The electrokymographic findings in valvular heart disease are of great physiologic significance. The phenomenon of atrial systolic plateau in mitral and tricuspid regurgitation may become a useful method of evaluating the apical systolic murmur.

In congenital heart disease electrokymography promises to be helpful in studying the status of the pulmonary artery circulation, particularly if the instrument is successfully calibrated as now appears to be the case. Investigations now in progress hold great promise that two of the most urgently needed clinical tests of cardiac function may be solved by electrokymography, namely, simple determinations of cardiac output and pulmonary artery pressure. Success in these fields would replace cumbersome, costly and hazardous technics by a relatively simple procedure.

In bundle branch block, Wolff-Parkinson-White syndrome and the various cardiac arrhythmias the electrical and mechanical events of the cardiac cycle can be correlated. Observations were presented concerning the relationship between length of diastolic interval, interval between auricular and ventricular systole, the strength and amplitude of cardiac contraction and the intensity of the heart sounds.

It was pointed out that the method can be of diagnostic aid in differentiating mediastinal and lung tumors from vascular or cardiac aneurysm.

In our opinion, the results presented in these reviews justify further intensive studies with the electrokymograph. Continued study will eventually simplify the instrument, expand its usefulness and provide another valuable aid in the study of cardiac physiology and disease.

REFERENCES

1. Dack, S. and Paley, D. H. Electrokymography. I. The ventricular electrokymogram. *Am. J. Med.*, 12: 331, 1952.
2. Willis, K., Eddleman, E. E., Jr., Acker, J. K., Poulos, E. and Heyer, H. E. Variations in the duration of phases of the cardiac cycle in normal hearts as studied by the electrokymograph. *Am. Heart J.*, 40: 485, 1950.
3. Heyer, H. E., Willis, K. and Eddleman, E. E., Jr. Great vessel motion. Electrokymography, Proceedings of the First Conference, 39, 1950.
4. Wiggers, C. J. Physiology in Health and Disease, ed. 5, p. 666. Philadelphia, 1949. Lea and Febiger.
5. Luisada, A. A. Pulsations of the pulmonary vessels. Electrokymography, Proceedings of the First Conference, 65, 1950.
6. Luisada, A. A., Fleischner, F. G. and Rappaport, M. B. Fluorocardiography (electrokymography). II. Observations on normal subjects. *Am. Heart J.*, 35: 348, 1948.
7. Henny, G. C. and Boone, B. R. Electrokymograph for recording heart motion utilizing the roentgenoscope. *Am. J. Roentgenol.*, 54: 217, 1945.
8. Mednick, H., Schwedel, J. B. and Samet, P. Electrokymographic studies of the normal cardiac cycle. *Circulation*, 2: 250, 1950.
9. Luisada, A. A. and Fleischner, F. G. Temporal relation between contraction of right and left sides of the normal human heart. *Proc. Soc. Exper. Biol. & Med.*, 66: 436, 1947.
10. Luisada, A. A. and Fleischner, F. G. Dynamics of the left auricle in mitral valve lesions. *Am. J. Med.*, 4: 791, 1948.
11. Luisada, A. A. Atrial phenomena. Electrokymography, Proceedings of the First Conference, 53, 1950.
12. Engström, B., Kjellberg, S. R., Persson, L. and Rudhe, U. Some aspects of use of electrokymography in cardiac investigations. *Acta radiol.*, 31: 435, 1949.
13. Lian, C., Facquet, J. and Minot, G. La radio-electrokymographie; interpretation des courbes physiologiques, application au probleme des cardiopathies valvulaires mitrales. *Arch. d. mal. du coeur*, 41: 727, 1948.

14. Soulie, P., DiMatteo, J. and Marchal, M. La cinedensigraphie dans les valvulites mitrales. Regurgitation systolique auriculaire. *Arch. d. mal. du coeur*, 43: 14, 1950.
15. McKinnon, J. B. and Friedman, B. Electrokymographic studies of the left atrium in normal and diseased hearts. *Circulation*, 2: 572, 1950.
16. Heyer, H. E., Poulos, E. and Acker, J. H. Electrokymographic studies in insufficiency of the aortic and pulmonic valves. *Circulation*, 1: 1037, 1950.
17. Jorgens, J., LaBree, J. W., Adams, F. H. and Veasy, L. G. An electrokymographic study of the pulmonary pulsations in congenital heart disease. *Bull. Univ. Minnesota Hosp. & Minnesota Med. Found.*, 31: 243, 1950.
18. Grishman, A., Kroop, I. G., Steinberg, M. F. and Dack, S. Presystolic pulsations of the liver in the absence of tricuspid disease. *Am. Heart J.*, 40: 731, 1950.
19. Grishman, A., Brahms, S. A., Gordon, A. and King, F. H. Aberrant insertion of pulmonic veins. *J. Mt. Sinai Hosp.*, 17: 336, 1951.
20. Teschendorf, W. Lehrbuch der Roentgenologischen Differentialdiagnostik der Erkrankungen der Brustorgane. Leipzig, 1939. Georg Thieme.
21. Ellinger, G. F., Gillick, F. G., Boone, B. R. and Chamberlain, W. E. Electrokymographic studies of asynchronism of ejection from the ventricles; normal subjects and patients with bundle branch block. *Am. Heart J.*, 35: 971, 1948.
22. Dack, S., Paley, D. H. and Brahms, S. A. The electrokymogram in Wolff-Parkinson-White syndrome. *Am. Heart J.*, 41: 437, 1951.
23. Samet, P., Mednick, H. and Schwedel, J. B. Electrokymographic studies of the relationship between electrical and mechanical asynchronism in the cardiac cycle. *Am. Heart J.*, 39: 841, 1950.
24. Paley, D. H., Brahms, S. A. and Dack, S. Electrokymographic findings in bundle branch block. To be published.
25. Scherlis, L. and Grishman, A. Spatial vectorcardiography: Left bundle branch block and left ventricular hypertrophy. II. *Am. Heart J.*, 41: 494, 1951.
26. Chamberlain, W. E. Discussion. Electrokymography, Proceedings of the First Conference, 111, 1950.
27. Phillips, E., Discussion. Ibid, p. 116.
28. Dack, S., Paley, D. H. and Brahms, S. A. Ventricular contraction in Wolff-Parkinson-White syndrome: An electrokymographic study. *Bull. New York Acad. Med.*, 26: 273, 1950.
29. Samet, P., Mednick, H. and Schwedel, J. B. Electrokymographic studies of the relation between the electrical and mechanical events of the cardiac cycle in Wolff-Parkinson-White syndrome. *Am. Heart J.*, 40: 430, 1950.
30. Grishman, A., Kroop, I. G. and Steinberg, M. F. The course of the excitation wave in patients with electrocardiograms showing short P-R intervals and wide QRS complexes (Wolff-Parkinson-White Syndrome); an analysis based on studies with intracardiac and esophageal leads. *Am. Heart J.*, 40: 554, 1950.
31. Sussman, M. L., Dack, S. and Paley, D. H. Some clinical applications of electrokymography; the findings in myocardial infarction and heart block. *Radiology*, 53: 500, 1949.
32. Harvey, W. P. and Levine, S. A. The changing intensity of the first sound in auricular flutter, an aid to the diagnosis of auscultation. *Am. Heart J.*, 35: 924, 1948.
33. Rytand, D. A. The variability of the first sound in auricular fibrillation. *Am. Heart J.*, 37: 187, 1949.
34. Dack, S. and Paley, D. H. An electrokymographic study of ventricular contraction and its effect on the heart sounds in auricular fibrillation. Presented at the Scientific Session of the New York Heart Assoc., April 11, 1950. To be published.
35. Westermark, N. On the circulation through the heart, the big vessels and pulmonary circulation simultaneously recorded by cinematography and electrocardiography. *Acta radiol.*, 23: 475, 1942.
36. Sussman, M. L. and Grishman, A. Discussion of Angiocardiography and Angiography. Advances in Internal Medicine, vol. 2, p. 102. New York, 1947. Interscience Publishers, Inc.
37. Lian, C., Minot, G. and Welti, J. J. Phonocardiographie; auscultation collective, p. 197. Paris, 1941. Masson et Cie.
38. Wolferth, C. C. and Margolies, A. Influence of auricular contraction on the first heart sound and the radial pulse. *Arch. Int. Med.*, 46: 1048, 1930.
39. Dock, W. Mode of production of the first heart sound. *Arch. Int. Med.*, 51: 737, 1933.
40. Dock, W. Further evidence for the purely valvular origin of the first and third heart sounds. *Am. Heart J.*, 30: 332, 1945.
41. Pordy, L., Kolker, J. and Levy, H. Paroxysmal ventricular tachycardia of prolonged duration. *Am. J. Med.*, 10: 254, 1951.

Seminars on Congenital Heart Disease

The Patent Ductus Arteriosus*

Observations on Diagnosis and Therapy in 525 Surgically Treated Cases

ROBERT E. GROSS, M.D.

Boston, Massachusetts

FROM a historical standpoint surgical treatment of the patent ductus arteriosus is a fascinating chapter in modern therapeutics because it formed the opening wedge in the surgical attack on congenital cardiovascular anomalies. From a more practical point of view the diagnosis and treatment of the persistent ductus has become of considerable importance because it is now generally acknowledged that the abnormality can be detected with great accuracy and can be treated surgically with very satisfactory results. The following presentation is based upon a rather extensive experience with the condition during the last thirteen years, during which 525 patients have been operated upon by myself or by my associates and residents.

CLINICAL FINDINGS

Patent ductus arteriosus is much more common in females (70 per cent in our series). Subjects with an open ductus may have little or no evidence of cardiac embarrassment; or conversely, they may have marked invalidism, depending upon the age of the person and the size of the shunt which exists. In general, the abnormality is tolerated well in childhood and decompensation is rare in that period. As a rule, youngsters have endless energy, can indulge in strenuous sports and are thought to be entirely normal by their parents. In some instances there is slight to moderate limitation of physical activity; strenuous exercise is followed by dyspnea, palpitation and excessive fatigue.

In an important percentage of childhood cases, but not in the majority of them, the general physical development is somewhat retarded. When compared with normal children of the same age, the height and particularly the weight are distinctly less than the average; in some instances these findings are very striking. In no child have we seen lack of mental development which could be rightfully ascribed to the presence of an open ductus.

Patients in mid-life often have moderate cardiac embarrassment; less commonly they have the classical findings of failure. Adults frequently find that they cannot maintain former levels of work, that fatigue is marked or that long periods of rest are required. There are a considerable number of individuals who present themselves in their thirties or forties who have no frank symptoms or signs of cardiac failure but who, nevertheless, have lost their "pep" and who drag about in their daily existence with no exuberance. While such people are by no means invalids in the common sense of the term, they are incapacitated and are limited in their effectiveness and usefulness.

The physical findings in a case of uncomplicated patent ductus arteriosus are clear-cut. It is important to emphasize that simple examination (with stress upon intelligent auscultation) can lead to rapid and accurate recognition of this congenital abnormality in more than 95 per cent of the cases.

The color of the skin and the mucous membranes is normal in most instances but some pallor is present in others. Cyanosis is never found unless there is frank cardiac failure and a reversal of blood flow through the ductus, a situation found only in terminal cases. The nails are not clubbed. The heart is normal or slightly increased in size; great enlargements are rare.

* From the Department of Surgery of the Harvard Medical School and the Surgical Services of the Children's Hospital and the Peter Bent Brigham Hospital, Boston, Mass.

The cardiac activity may be within normal limits but if the ductus is large there is increased forcefulness of the impulse and a heaving pulsation over the neck vessels. These findings are more apparent in thin subjects than in those who are heavy-set.

Ductus patients usually have systolic blood pressures which are normal for their respective ages. The diastolic level is apt to be depressed, depending upon the size of the aortic leak. Small fistulas do not give any important change in the diastolic pressure but large ones are accompanied by diminution to 50 or 40 mm. of mercury. When the pulse pressure is high, there may be a Duroziez's sign or a visible capillary pulsation in the nail beds.

The femoral arterial pulsations are excellent, the pressures in the legs being above those of the arms; points of importance in ruling out coarctation of the aorta.

By auscultation a very characteristic murmur is heard in the second or third intercostal space to the left of the sternum. (It is heard better and more intensely with a large flat (Bowles) chestpiece than with a cone-shaped (Bell) attachment.) It is continuous, is accentuated during systole and dies off during diastole: it usually has a rumbling quality. The pulmonic sounds may be replaced by the murmur, or the second sound may be quite accentuated. The murmur has been well described as a "machinery" murmur, and the physician who has heard it several times should always be able to recognize it thereafter. It may be widely transmitted over the precordium, into the left axilla, up into the neck or over the back, particularly to the left of the spine. While all of the murmur might be transmitted, it is more common to have only the louder, systolic portion carried to the cardiac apex, to the neck or to the back.

Generally speaking, any loud systolic murmur (unaccompanied by a diastolic element) in acyanotic congenital heart disease comes from a septal defect or from a pure pulmonic stenosis. Rarely, it is possible for a tiny ductus to produce a murmur which is limited to systole: the murmur is of rather low intensity (roentgen study of the heart will show little or no variation from the normal). Also, in other rare cases it is possible for an exceedingly large ductus to produce only a systolic murmur because the pulmonary artery pressure mounts so high that there is flow through the ductus only at the height of the systolic surge (such a patient almost certainly has considerable cardiac incapacitation and by roentgen study has a large heart and a very prominent pulmonary artery). In both of these situations with only a systolic murmur—of either a very tiny or an exceedingly large ductus—cardiac catheterization is necessary to clarify the diagnosis. It is well to emphasize that patients with solely a systolic murmur constitute only a few per cent of any ductus series. Since more than 95 per cent of all ductuses gives a continuous murmur, the diagnosis of a patent ductus should not be made in the absence of such a murmur unless this can be supported by incontrovertible evidence from catheterization studies.

The classical sounds of an open ductus may not be found if one is examining a patient (usually an adult) during cardiac failure. At that time the pulmonary artery pressure may be exceedingly high so that a near-equalization between it and the aortic tension gives a reduced ductus flow, no flow at all or even a reversal of flow. Such conditions will give, respectively, a murmur limited to systole, no murmur, or a variable murmur associated with intermittent cyanosis. A good description of such a case has been presented by Johnson et al.[11]

A ductus murmur is generally one of considerable intensity, is indicative of a marked turbulence in the pulmonary artery, and hence is often accompanied by a thrill which can be felt in the precordium. About half the patients have a thrill. It may be continuous or it may be limited to systole: it is most intense over the pulmonic region, and it is seldom felt far from this area.

Streptococcus viridans infection, superimposed upon an open ductus, is rarely found in childhood, although we have seen it as early as four years of age. The peak incidence of endocarditis or pulmonary endarteritis comes in the third and fourth decades, following which time the frequency diminishes. The findings include fever, persistent sweating, anorexia, weight loss, chest pain and phenomena in various parts of the body suggesting arterial embolism. The latter almost certainly indicate that vegetations are not limited to the ductus region but that they are present on the mitral or aortic valves. Blood cultures provide positive proof of blood stream infection, and they probably give some information regarding the severity of the invasion.

LABORATORY DATA

These patients do not have polycythemia.

Electrocardiographic tracings are helpful in a surprisingly small percentage of cases. They are of no assistance in establishing the diagnosis of a patent ductus. However, they are an important part of the study of patients suspected of having a ductus. First, they might give evidence to indicate that the subject actually has some other form of cardiovascular anomaly. Second, if a ductus actually exists, the tracings can give some idea of the extent of myocardial strain or damage.

In the vast majority of cases, particularly in children, electrocardiograms are normal and there is no axis deviation. In some tracings, particularly from adults, there may be a left axis shift, especially in the presence of a shunt of moderate or large size. Fibrillation or indications of myocardial damage may be found in some of the older subjects when the cardiac strain has been excessive.

Electrocardiographic study is most valuable as a method of excluding cases with other cardiac lesions. Particular attention should be given to the presence of any right axis deviation, the finding of which should make one strongly suspect some other anomaly such as a pulmonic stenosis or a tetralogy of Fallot. In only six patients have we found right preponderance when there was a pure patent ductus arteriosus; possibly the flow into the pulmonary circuit was very high or else there were secondary vascular changes in the lung bed, either of which could make the right ventricle hypertrophy as it pumps against an increased pressure.

Whenever a prolonged P-R interval is encountered, one should suspect that the auriculoventricular conduction apparatus is longer than normal and is probably stretched out around a septal defect.

Cardiac catheterization can give direct measurement of various blood flows, and can give a reasonably accurate idea of the size of the shunt, but it is not necessary as a routine study for average cases. There are many patients with obscure abnormalities of the heart who should be studied in every way possible, including catheterization, but it has been our experience that it is extremely rare to pick from this group a ductus which can come to operation which could not have been recognized by simpler means of roentgenography and cardiac auscultation. The details of catheterization technic and the results of such studies are authoritatively given in this symposium by Cournand and his associates.[4]

More than 95 per cent of patent ductuses can be recognized with great facility and rapidity. If a characteristic murmur does not exist in a given patient, too much reliance should not be laid on laboratory or roentgenologic findings (other than catheterization) which might suggest the presence of a ductus, because thoracic exploration under such circumstances will generally lead to the finding of some other cardiovascular defect.

ROENTGENOLOGIC CHANGES

Roentgenologic studies often help in the recognition of a patent ductus arteriosus: film and fluoroscopic observations are also valuable in ruling out other cardiac abnormalities and rheumatic valvular disease. With a pure patent ductus the findings are those of a shunt from the aorta into the pulmonary circuit. The heart is slightly or moderately enlarged, particularly in transverse dimension; marked enlargement is rare. While it may be difficult to tell whether there is hypertrophy (or dilatation) of one or both ventricles, not infrequently it is possible to show that the left chamber is the predominant one. Often the pulmonary artery (sometimes incorrectly called the pulmonary conus) is fuller than normal and projects outward from the left border of the cardiac shadow. Likewise, vessels within the lung fields, particularly in the hila, are apt to have increased fullness. In about half the cases the central vessels of the lungs show a "hilar dance"; this may be quite difficult to observe and too much stress should not be placed upon the presence or absence of this point. Left anterior oblique and lateral views show left auricular enlargement in about half of the cases; this is best seen as an encroachment on the barium-filled esophagus. Such enlargement is dependent upon an increased flow through the left side of the heart; the left ventricle enlarges somewhat whereas the thin-walled auricle dilates to a considerable degree. Fluoroscopic observations and kymographic tracings generally show increased expansion and contraction of the left ventricle as well as increased pulsations of the aortic knob and pulmonary artery.

The roentgenologic changes are not specific for patent ductus arteriosus; they may be

mimicked by certain other lesions. Septal defects are left-right shunts which give the findings of increased pulmonary flow. A fenestrum between the first portions of the aorta and pulmonary artery gives roentgenologic pictures exactly like those of an open ductus. When the roentgenologist finds evidence of a left-right shunt, he is faced with the possibility of making several diagnoses. If, in addition to augmented pulmonary flow there is right ventricular enlargement, he should lean toward a diagnosis of interventricular septal defect. If there is an associated right auricular enlargement, an interauricular septal defect is suggested. If there is no enlargement of the right side of the heart, he can be reasonably sure that the patient has a patent ductus arteriosus (or one of the rare defects between the first portions of the aorta and the pulmonary artery).

If a ductus is small, the roentgenologic picture is normal or shows little change therefrom. Conversely, when a ductus is of moderate or large size the roentgenologic findings are clear-cut and striking.

Elsewhere in this symposium the angiocardiographic findings of an open ductus are presented in detail by Dotter and Steinberg.[16]

DIFFICULTIES OF DETECTION IN INFANCY

Parents are often disturbed by the fact that a physician did not detect a cardiovascular abnormality in their child in the first few years of life. It is important to restore confidence in their doctor by pointing out that often it is utterly impossible to hear a murmur in infancy. While it is true that some babies with a ductus have a continuous and easily recognizable machinery murmur from birth, it is more common to find the following series of events: In the early months the aortic pressure is low and the pulmonary pressure is normally high; there is no appreciable flow through the ductus and there is no murmur. In the subsequent year or so the aortic pressure rises and the pulmonary pressure falls; there is some ductus flow and there is a systolic murmur. By the third year the aortic pressure is high and the pulmonary pressure is low; there is now a considerable ductus flow and a typical continuous murmur. From these facts it is obvious that the best of physicians might not have been able to hear anything unusual in early life.

From the above considerations it is clear that if one examines a child with congenital heart disease in the first year or two of life and hears only a systolic murmur it is not possible to exclude a ductus; under such circumstances it is important to examine the child again at three or four years, because if a ductus is present it will by that time produce a continuous type of murmur.

PREDICTION OF THE SIZE OF THE DUCTAL SHUNT

By cardiac catheterization it is, of course, possible to make a reasonably accurate estimate of the blood flow through an open ductus. Without catheterization it is still possible—in a rough way—to gain some impression of whether one is dealing with a ductus of small, medium or large size. (1) If the heart is normal in size or is only slightly enlarged, if the beat is not overly vigorous, if the x-ray changes are minimal and if the diastolic pressure is only slightly diminished, it is reasonable to assume that the shunt is a relatively small one. (2) If the heart is definitely enlarged, the murmur is intense and perhaps accompanied by a thrill, the diastolic pressure is moderately depressed, and the fluoroscopic findings indicate a considerable left-right shunt, one can assume that the ductus is of average size. (3) In rare cases (possibly one of thirty or forty patients) the heart is quite enlarged, there is a heaving beat which shakes the patient's chest or even the bed on which he lies, there are forceful pulsations in the neck, there are marked fluoroscopic changes, and the diastolic pressure is greatly depressed (although in a few instances the pulmonary pressure may be so high that the peripheral diastolic pressure is not particularly low); one can instantly predict that the shunt is of tremendous size. Under these latter circumstances one is apt to hear additional murmurs which are indicative of a greatly augmented flow through the left side of the heart; the large amount of blood (which may be two or two-and-a-half times normal) will set up murmurs as it rushes through the orifice of a normal mitral or a normal aortic valve. Therefore, in addition to the continuous murmur of the ductus in the pulmonary zone one can hear a separate diastolic murmur in the mitral area, or a separate systolic murmur in the aortic region. It is important to recognize these occasional cases with tremendous shunts so that the patient's family can be informed of the risks, which are much higher than those of average cases. Also the surgeon can be adequately prepared to deal with a situation which will present

technical difficulties enormously greater than those which are ordinarily encountered.

DIFFERENTIAL DIAGNOSIS

On clinical grounds it is extremely difficult to differentiate between an open ductus and a window between the first parts of the aorta and pulmonary artery. Both are left-right shunts and give rise to quite similar murmurs and roentgenologic findings. It is virtually impossible to differentiate between the two conditions by angiocardiography when the dye is injected by the venous route; it has been possible to visualize an aortic septal defect by retrograde arterial injection.[7] By catheterization, differentiation is impossible unless fortuitously the catheter can be passed through the existing shunt.[5] Aortic septal defects are about 1 or 2 per cent as common as open ducti. They have been exposed at the operating table[8]—in the belief before operation that the patient actually had a patent ductus. In one patient we have been able to close such an opening.[10]

It is worth describing a small group of patients who have high interventricular septal defects which lie in such a position that the medial cusp of the aortic valve is incompletely supported, and hence collapses from time to time and gives aortic valve regurgitation. We have seen twelve such cases (about one to every forty-five ductus patients). The murmur is most intense in the pulmonary area but it does not have a truly continuous quality. It is more properly described as a "to-and-fro" murmur, which on occasion can be exceedingly difficult to differentiate from the continuous murmur of an open ductus. There is a marked tendency for the murmur to change in character from time to time. Patients with these high septal defects have a very low diastolic pressure (because of the aortic valve insufficiency), important A-V conduction defects by electrocardiographic tracings, and greatly increased pulsations of the aortic arch and pulmonary arteries by fluoroscopic study.

Interventricular or interauricular septal defects can generally be readily differentiated from an open ductus by the fact that the murmur is more centrally located and is sharply limited to systole.

A pure pulmonary stenosis gives a murmur in the pulmonary area but it is clearly limited to systole, is accompanied by marked right preponderance in the electrocardiograms, and has quite characteristic findings by roentgenographic study.

PROGNOSIS IN UNTREATED CASES

Whenever a ductus remains open beyond the neonatal period, the individual has a shunt which is somewhat similar to an arteriovenous fistula. The communication may be tolerated extremely well if the possessor is fortunate enough to escape superimposed infection and if the shunt is a small one so that the work of the heart is not greatly increased. With such favorable circumstances, patients have been known to live to advanced age, with little or no incapacitation, but such a happy outcome is not encountered very often. Certain hazards are apt to occur frequently in patients with an open ductus: (1) The shunt may divert so much blood from the aorta that the peripheral circulation is deficient; the individual has a retarded physical development. (This diminished arterial flow never causes mental deterioration; whenever mental retardation is seen in a ductus patient, the brain damage almost certainly is related to some other factor.) (2) The heart may increase its output, attempting to maintain the peripheral flow at a satisfactory level while passing a large amount of blood back through the shunt; if these two things are accomplished, the heart is tremendously overworked. The individual may be well developed but the heart will probably come to embarrassment or failure. (3) Bacterial infection may be superimposed upon the vascular abnormality, the causative organism commonly being the Streptococcus viridans. In patients who have been followed over sufficiently long periods of time the incidence of this complication is probably 25 per cent. (4) There are rare complications such as aneurysmal dilatation or rupture of the ductus. The first of the above named complications appears in childhood whereas the others are more apt to be problems of adult life, particularly of the third and fourth decades.

While a patent ductus usually seems to be an innocuous affair in childhood, long-term observations show that commonly the outlook is serious because of the likelihood of late incapacitation and shortening of life. An excellent study of the prognosis for patients with an untreated ductus has been made by Keys and Shapiro.[12] They find that subjects who are alive at seventeen years of age have a subsequent life

expectancy which averages only about half that of the general population.

SELECTION OF PATIENTS FOR OPERATION

Regarding the decision for or against operation, the following general policies have been developed and adopted:

Certainly, there can be no disagreement with the recommendation that operation be undertaken for all children with retarded physical development which cannot be accounted for on some other basis. Likewise, it is generally agreed that cardiac fatigue or failure demands operative closure of the shunt regardless of age so that the mechanical burden on the heart can be reduced. Operation is also desirable for those subjects—mostly in the third and fourth decades—who do not show ordinary signs of cardiac failure but who nevertheless drag about with fatigue, reduced activity, and definite knowledge that it is becoming increasingly difficult to carry on the job of life.

Regarding the possible benefits of surgery for patients who have blood stream infection with Streptococcus viridans, opinion has taken several turns during the past decade. Prior to 1940 this serious malady could not be cured in more than 5 or 10 per cent of cases with the sulfonamides and other measures which were then available. In 1940 Touroff and Vesell[17] showed in a very dramatic way that such infection could be cured in about 75 per cent of the cases by surgical obliteration of the ductus, even without concomitant sulfonamide therapy. We corroborated this with nine recoveries in twelve infected patients who were surgically treated in the pre-penicillin era. With the advent of penicillin in the mid-forties, such recovery rates could be equaled, or even bettered, by penicillin therapy alone. This might seem to indicate that the infected patient should be treated solely by penicillin, aureomycin, chloromycetin or other antibiotic, but two important factors should be taken into account. First, it is known that subsequent attacks are not uncommon and it is possible that a second infection might come from an organism which is resistant to chemotherapy. Second, while it is possible to cure infection in a high percentage of cases by appropriate chemotherapy, this does not necessarily mean that the entire cardiac mechanism can be returned to normal. Patients whose infections have been dispelled are sometimes left as cardiac invalids by the scarring which remains in the myocardium. Because infection always leaves some myocardial damage, it is highly desirable to reduce the mechanical load of the heart by surgically closing the open ductus. It is our present day opinion that: (1) Infected patients should be intensively treated by chemotherapeutic means for an appropriate length of time. If the blood stream cannot be sterilized by this alone, operation should be added during the active stage. (2) If it is possible to sterilize the blood stream by drugs alone—which can be accomplished in about four-fifths of the cases—operation can be deferred for several months. This delay in operation permits inflammatory reactions in the ductus wall to subside and thus lessens the technical difficulties of surgery. It also allows the patient to recoup somewhat from the financial onslaught of an attenuated illness. It permits him to get out of the hospital for a period and to convalesce satisfactorily before undertaking a major operation. In summary, all infected cases should be treated by chemotherapy plus surgery, the latter being either early or delayed, depending upon the inadequacy or efficacy of drug treatment.

After a consideration of the above three categories (the physically retarded youngster, the patient with cardiac failure or fatigue and the subject with superimposed infection) one is left with a large number of patients—particularly in the childhood ages—who have no important symptomatology and who repeatedly raise the question of whether or not operation should be advised. The answer to this query depends almost entirely upon the fatality rates and the promise of a permanent ductus closure which can be offered by the surgeon. In a large series of such patients we have been able to demonstrate that permanent closure can be assured by division of the ductus, that complications are almost nil and that fatalities are distinctly less than 0.5 per cent. With this record, we feel fully justified in advising surgical closure of the ductus for all children and young adults, even though they are symptom-free at the moment. Without doubt, this approach will mean subjection to operation of some individuals who admittedly might be fortunate enough to go through a long life with no important troubles from a small, open ductus. However, when considering the group as a whole, there can be no question about the fact that many future com-

plications (such as cardiac fatigue and endarteritis) can be prevented by operating upon these subjects.

A few clinicians believe that it is preferable to avoid surgery for all who are asymptomatic, employing it only for those who develop complications in later years. This attitude certainly increases the surgeon's difficulties. Ductus operations in the young can be performed with relative ease whereas those in older people give much anxiety because the cardiac reserve is reduced, the approach into the mediastinum is deeper, the regional vessels are more rigid and much more difficult to deal with.

We are strongly impressed by the number of patients who had been entirely asymptomatic in childhood and in their teens but who then present themselves in middle life with symptoms which physicians would universally agree call for operative intervention. Operations on these older subjects do not carry higher fatality rates in our series but they certainly tax the surgeon's ingenuity. A few experiences of this kind certainly indicate that it is far wiser and easier to operate upon patients in earlier life when the cardiac reserve is greater, the operative exposure is simpler and the regional vessels are softer, elastic and much easier to work upon. In summary, we believe that it is good "prophylaxis," which can be obtained at a negligible mortality rate, to advise surgical closure of the ductus for all children and young adults even though they have no complaints at the moment.

Finally, what advice should be given those rather rare patients beyond thirty or thirty-five years of age who have always been symptom-free? Generally, these have small shunts (the larger ductuses having proved fatal in earlier life); the mechanical burden on the heart is therefore usually light. Furthermore, these people, while not entirely free from the possibility of superimposed bacterial infection, have passed the years of peak incidence of this complication; it is becoming a decreasing menace for them. These considerations, plus the fact that operation in this time of life is certainly not easy, probably make it wise to avoid operations beyond mid-life. (This attitude for the asymptomatic middle-aged and elderly subjects should in no way make one hesitate to proceed with operation for anyone who has important symptoms in advanced years. We have operated upon a woman of fifty-one with marked incapacitation who was tremendously benefited by surgery.)

An associated interventricular or interauricular septal defect is not a contraindication to surgical closure of an open ductus. A ductus does not compensate for either of these anomalies; all three anomalies are left-right types of shunts. Obviously, operation on a patient with an open ductus and a septal defect will not restore the cardiovascular apparatus to normal but at least the heart can be considerably improved by taking off some of its mechanical burden. We have operated upon twenty-one such patients, all of whom survived.

Rheumatic mitral stenosis is not a contraindication to operative closure of the ductus, provided there is no important rheumatic activity at the time operation is undertaken. Indeed, an associated rheumatic mitral stenosis is a clear-cut indication for surgical closure of the ductus because such therapy will reduce the amount of blood which has to flow through the left side of the heart and the narrowed valve. Obviously, under these circumstances the cardiovascular apparatus cannot be made normal but it can certainly be improved. We have operated upon four such individuals, all of whom survived.

The combination of pulmonary stenosis and a patent ductus is rare; it is not a contraindication to operation on the latter. A ductus in no way compensates for the bottleneck at the pulmonic valve (in contrast to the compensatory effects of a ductus on the tetralogy of Fallot). Operative closure of the ductus is a desirable procedure, even though it will not return the cardiovascular apparatus to normal. We have operated upon three children with this combination of abnormalities; all survived. If in future years the pulmonary stenosis is of sufficient degree to produce important symptoms, the pulmonary orifice can be enlarged by the Brock technic.

A word of caution is necessary regarding individuals who have any cyanosis and who also have the auscultatory sounds of a patent ductus arteriosus. With these findings the ductus should never be closed surgically; either the patient is one in terminal failure from a large ductus or else there is a ductus which is acting as a compensatory mechanism for a complicated cardiovascular defect.

A consideration of the indications for operation should include some comment regarding the ages during which it is preferable to under-

take this form of surgery. In general, if there are pressing indications for operation such as stunting of physical growth, cardiac embarrassment or superimposed infection, therapy should be undertaken with complete disregard for the age or size of the patient. We have operated upon an eleven month old baby who weighed but 13 pounds, who had marked physical retardation and also cardiac failure; at the other end of the scale a woman of fifty-one was operated upon because of marked pulmonary hypertension and incapacitation. Both of these patients had excellent recoveries. Regarding operation on asymptomatic subjects, operation can be performed within a wide span of years. While it is quite possible to do so, there is seldom need for proposing such a step before three or four years. The surgeon still has excellent vessels to work upon until fifteen or twenty years of age although this limit is by no means a sharp one. In short, for the elective cases optimum ages run from three or four years up to fifteen or twenty years; the best chances for a smooth and relatively easy surgical procedure are generally provided between the ages of six and twelve.

SURGICAL TECHNIC FOR DUCTAL CLOSURE

Omitting all operative details, only a few general statements have to be made here regarding surgical procedures.

Formerly we employed cyclopropane anesthesia for these cases but since about half of our fatalities seemed to have been attributable to cardiac arrest or irregularity under this anesthetic we have now completely abandoned cyclopropane and employ ether and oxygen as a routine. Obviously, the anesthesia must be given with a closed system. An intralaryngeal tube should be used to ensure an adequate airway at all times and to facilitate the suction removal of any secretions from the lower respiratory tract. This gives the best chance for maintaining a quiet anesthesia and it reduces the incidence of postoperative pulmonary complications.

There are some who have employed a posterior thoracic approach, an exposure which seems to us to be unduly complicated and quite unnecessary for the average ductus case. It requires a more time-consuming exposure and closure. It certainly does not give the best view of the ductus. Its only possible superiority would be in the rare case with a huge ductus for which one might want to place a large Potts-Smith-Gibson or a Freeman clamp on the aorta to isolate the ductus area without completely occluding the aortic lumen; such an application is impossible or is awkward from the anterolateral approach. In all of our cases the chest opening has been through a left anterolateral incision, made below the breast for cosmetic reasons, cutting the third intercostal muscles all the way around to the angle of the ribs. When handling adults, or when dealing with patients with large ductuses in whom maximum exposure is desirable, the incisions of the skin, the latissimus dorsi muscle, and anterior serratus muscle should be carried as high in the axilla as possible and well around to the posterior axillary line. This exposure has been so satisfactory that we see little reason for changing it.

When the mediastinum is entered in front of the lung root, thorough knowledge of the local anatomy and of the congenital abnormalities which are apt to be encountered in this region is indispensable. In so crowded a space a single false step can lead to disaster. Probably the greatest cause of failure in this type of surgery has been the trepidity of those who are unsure of the exact positions of the large vessels; being fearful of setting up an uncontrollable hemorrhage, they do not adequately free the ductus from its surrounding vestments. If the ductus has been incompletely liberated, it is subsequently almost impossible to work on it with any assurance of performing a satisfactory closure. Conversely, an accurate anatomic knowledge of the area will allow one to proceed rapidly and without risk, to free the ductus entirely of all its coats, to clean off the adjacent aorta and to mobilize adequately the nearby pulmonary artery. Only by such an extensive and thorough freeing can one deal with the ductus in a proper manner.

In the earlier part of our work only ligation of the ductus was employed, using various types of material to accomplish this. In a series of forty-three cases it was found that 80 per cent of the patients obtained a complete obliteration and permanent closure of the shunt, 10 per cent had the ligatures cut through and some of the fistula re-established, and the remaining 10 per cent had ligatures which were not put on tightly enough to close the vessel completely. While these over-all results might be considered satisfactory, it is obvious that they were not perfect. These observations are similar to those of Shapiro and Johnson[15] who analyzed (by personal communications with various physicians) 626 pa-

tients operated upon by forty-six surgeons; the mortality rate in uninfected cases was 4.9 per cent and the incidence of recanalization was at least 8.7 per cent. Blalock[2] has developed a method of "suture-ligation" which is distinctly better than all of the ligation technics which we originally employed; it uses two encircling stitches at either end of the ductus, mattress sutures through the ductus and an encircling tape of linen. Scott[14] has recently published a series of 161 closures of this type with excellent results. However, it has been widely recognized by vascular surgeons for many decades that closure of any large artery or shunt is most satisfactorily accomplished by a complete severance of the vessel; we believe that this fundamental principle also applies to the treatment of an open ductus. Complete division certainly seems to be the ideal method of therapy, provided it can be accomplished without assuming a high risk.

While complete severance of a ductus would seem to be fraught with dangers of uncontrollable bleeding, we have demonstrated to our own satisfaction that as a routine procedure the vessel can be cut in half and separate closures made of its pulmonic and aortic ends. We have now performed 482 complete divisions without the loss of a single patient from hemorrhage at the time of operation or subsequent thereto. Obviously, the division technic requires more time and care at the operating table yet we have found it possible to turn over a large number of these cases to assistant residents on the thoracic service who have performed a division in every instance without a single fatal hemorrhage.

During the period in which we have divided the ductus in the 482 patients, we have explored (and withdrawn from) four who had enormous shunts (larger than 1.5 cm. in diameter); division seemed to be too formidable and risky; certainly any form of ligation or suture-ligation would have been ineffective and probably fatal because of vessel erosion and bleeding. For these rare shunts of great size (a little less than 1 per cent in our series) some special procedure must be developed, such as that suggested by Freeman and more recently by Conklin and Watkins.[3]

The patient's postoperative course can be made quite comfortable by injection of a long-acting local anesthetic in the posterior portions of the upper four or five intercostal nerves while the chest is open. For the last twelve years we have routinely infiltrated nupercaine (in oil) about these structures, producing a regional hypesthesia which lasts for a week or ten days.

Careful closure of the chest has much to do with a patient's postoperative comfort. Meticulous hemostasis minimizes the accumulation of fluid within the pleural cavity. In all cases some fluid does collect in the pleural sac but in only a small percentage of subjects is this of sufficient degree to require postoperative tapping.

While chemotherapy is wholly unnecessary in many cases, there is some justification for using it as a routine prophylactic measure in the hope of avoiding postoperative pulmonary complications. It has long been our custom to give appropriate chemotherapy for twenty-four hours before operation and to continue it for four or five days thereafter.

Oxygen tents are not necessary during the postoperative period. If the left lung is completely expanded at the end of operation and if pleural fluid is kept at a minimum (by avoiding it or by aspirating any large collections), the respiratory apparatus is functionally adequate and an oxygen tent is a needless encumbrance.

Patients can be allowed out of bed on the fourth or fifth day and can be ambulatory shortly after that. Routinely they are discharged from the hospital on the eighth or ninth postoperative day. They are allowed increasing physical activity for the subsequent week or two, and ordinarily are back to complete and unrestricted activity or employment one month after operation.

RESULTS OF SURGICAL TREATMENT

At the present time the surgical closure of a patent ductus should seldom be followed by any serious complications; the mortalities should not be more than a few per cent. In our series 525 patients have been operated upon, 43 of whom had some form of ligation and subsequently 482 had complete division. In the latter group there have been ten fatalities, giving an over-all mortality rate of 2 per cent. This series included a considerable number of patients who had some degree of cardiac failure and also twelve who had active bacterial infection at the time of operation. In those patients who had only minor symptoms prior to operation the mortality rate has been less than 0.5 per cent.

In the surviving patients there have been

certain changes which can be individually considered as follows:

The diastolic blood pressure rises immediately, the extent of rise varying with the depression which had existed prior to operation.

In all cases the continuous machinery murmur disappeared following division of the ductus, and indeed in more than 90 per cent of subjects no murmur of any kind could be heard after the surgical undertaking. A small group have a soft systolic murmur which is believed to be functional. About 6 per cent have a residual murmur which undoubtedly comes from a second cardiac defect.

The activity of the heart strikingly diminishes after surgical closure of a ductus. This can be determined by inspection of the thorax, by noting reduced prominence in pulsations of the neck vessels and by fluoroscopic or kymographic studies. A heart which before operation had a heaving, pounding and forceful beat will be found to have a postoperative activity which in comparison is quiet and much less vigorous. Diminution in cardiac action is not great if the ductus was a small one; in contrast, obliteration of a large shunt is followed by a decrease in forcefulness which is quite evident to both physician and patient.

Some change in the over-all size of the heart can often be expected after closure of a shunt. Cardiac enlargement can represent hypertrophy or dilatation, but generally it is a combination of the two. If enlargement is due primarily to dilatation, this will disappear immediately following surgical closure of the shunt. If hypertrophy has existed, the heart apparently has little ability to shrink, but observations in a growing individual will show that the thorax and other body measurements increase whereas the heart grows very little during this period. After a year or two a normal cardiothoracic ratio becomes established. When a ductus shunt is small, there is little diminution in the size of the heart following operation; when a fistula of large size has been closed, the over-all dimensions of the heart will decrease markedly. We have seen shrinkage in transverse diameters of as much as 1.5 cm.

Individuals who had essentially normal physical development before operation show no important changes following surgery. However, underweight subjects, most of whom are in the childhood group, will often exhibit a surprising and gratifying gain in weight during the year or two following surgery. Apparently, closure of a shunt increases the peripheral flow of blood to the body and thereby improves the general physical state.

Data have been gathered relative to the changes in the circulation following closure of a patent ductus arteriosus. The figures all clearly indicate that obliteration of the shunt can greatly diminish the output of the left side of the heart. Presumably, the cardiac reserve is accordingly improved.

In the pre-penicillin era twelve patients were operated upon during infection with Streptococcus viridans. Nine of these survived and were cured whereas the others eventually died of their infectious disease. Now that penicillin and other chemotherapeutic agents are available these should be used in conjunction with surgery. We have employed surgery for six patients who already had been cured of infection by antibiotics. All of them have survived, and it is believed that closure of the shunt was of value in their rehabilitation.

For those children and young adults who have been operated upon for "preventive" reasons there is general agreement that they, or their families, feel better on psychologic grounds for having had the anomaly corrected. Many of these people had previously harbored a fear that something disastrous was hanging over their head and they were much relieved when this anxiety was removed—a consideration of no small significance. While no objective measurement can be made of what has been accomplished, it is quite reasonable to think that many of these individuals have been kept free of complications which might otherwise have developed. Our patients have been followed for periods as long as thirteen years after closure of open ducti; none has yet developed bacterial endarteritis or cardiac failure. A considerable number of the females have subsequently gone through normal pregnancies and deliveries.

Studies on patients who have been operated upon leave no doubt about the benefits of closure of the congenital fistula. Experiences from many sources clearly indicate the effectiveness of surgical treatment when various complications have already developed. It is our firm conviction, based on low surgical fatality rates, that it is also advisable to operate upon all children and young adults who have an open ductus, believing that this prophylactic procedure is of real value in warding off cardiovascular complications in later years.

REFERENCES

1. Adams, F. H. and Forsyth, W. B. The effect of surgery on the growth of patients with patent ductus arteriosus. *J. Pediat.*, 39: 330, 1951.
2. Blalock, A. Operative closure of the patent ductus arteriosus. *Surg., Gynec. & Obst.*, 82: 113, 1946.
3. Conklin, W. S. and Watkins, E., Jr. Use of the Potts-Smith-Gibson clamp for division of patent ductus arteriosus. *J. Thoracic Surg.*, 19: 361, 1950.
4. Himmelstein, A. and Cournand, A. Cardiac catheterization in the study of congenital cardiovascular anomalies. *Am. J. Med.*, 12: 349, 1952.
5. Dexter, L. Catheterization of the right heart in congenital heart disease. *Mod. Med.*, 17: 92, 1949.
6. Eppinger, E. C., Burwell, C. S. and Gross, R. E. Effects of patent ductus arteriosus on the circulation. *J. Clin. Investigation*, 20: 127, 1941.
7. Gasul, B. M., Fell, E. H. and Casas, R. The diagnosis of aortic septal defect by retrograde aortography. *Circulation*, 4: 251, 1951.
8. Gibson, S., Potts, W. J. and Langewisch, W. H. Aortic-pulmonary communication due to localized congenital defect of the aortic septum. *Pediatrics*, 6: 357, 1950.
9. Gross, R. E. Complete division for the patent ductus arteriosus. *J. Thoracic Surg.*, 16: 314, 1947.
10. Gross, R. E. Surgical closure of an aortic septal defect. *Circulation*, in press.
11. Johnson, R. E., Wermer, P., Kuschner, M. and Cournand, A. Intermittent reversal of flow in a case of patent ductus arteriosus. *Circulation*, 1: 1293, 1950.
12. Keys, A. and Shapiro, M. J. Patency of the ductus arteriosus in adults. *Am. Heart J.*, 25: 158, 1943.
13. Potts, W. J., Gibson, S., Smith, S. and Riker, W. L. Diagnosis and surgical treatment of patent ductus arteriosus. *Arch. Surg.*, 58: 612, 1949.
14. Scott, H. W., Jr. Closure of the patent ductus by suture-ligation technique. *Surg., Gynec. & Obst.*, 90: 91, 1950.
15. Shapiro, M. J. and Johnson, E. Results in surgery in patent ductus arteriosus. *Am. Heart. J.*, 33: 725, 1947.
16. Dotter, C. T. and Steinberg, I. Angiocardiography in congenital heart disease. *Am. J. Med.*, 12: 219, 1952.
17. Touroff, A. S. W. and Vesell, H. Subacute Streptococcus viridans endarteritis complicating patent ductus arteriosus. *J. A. M. A.*, 115: 1270, 1940.
18. Wangensteen, O., Varco, R. L. and Baronofsky, I. D. The technique of surgical division of patent ductus arteriosus. *Surg., Gynec. & Obst.*, 88: 62, 1949.

Clinico-pathologic Conference

Rapidly Progressive Hepatic Failure

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, J. H. (No. 201337), was a white female student, sixteen years of age, who entered the Barnes Hospital for the first time on September 15, 1951, complaining of swelling of the face and enlargement of the abdomen. The family history was irrelevant. At the age of twelve the patient had smallpox. Six months before admission to the hospital she had a severe "head cold and sore throat" which lasted about one week and from which she recovered apparently without sequelae. The systemic review was negative.

Four months prior to entry the patient noted increasing fatigue. Shortly thereafter her eyelids became swollen. During the next three months these symptoms persisted and were accompanied by swelling of the ankles and a gradual gain in weight. About three weeks before admission the patient developed anorexia and noted soreness in the right upper abdomen. Her face became quite puffy, swelling of the ankles increased and abdominal swelling appeared. She was admitted to an outside hospital where she remained for four days. During this period her blood pressure was noted to be elevated and albumin was found in her urine. On bed rest and a low salt diet the edema decreased. One week prior to entry to the Barnes Hospital the patient had a chill and her temperature rose to 100°F. Despite the fact that she was given penicillin her temperature continued to rise and the patient was again hospitalized in the outside institution. With continuation of penicillin therapy her temperature fell to normal, but swelling of the face, legs and abdomen recurred, and the patient developed nausea and vomiting. She was referred to the Barnes Hospital for further study. She denied ingestion of drugs, exposure to known toxins or parenteral injections prior to the onset of the present illness.

Physical examination on entry revealed the temperature to be 37.4°C., pulse 96, respirations 20 and blood pressure 170/80. The patient appeared acutely ill and was markedly jaundiced. A papular, acneiform eruption was present on the face, chest and arms. The eyelids were edematous. The pupils reacted well to light and accommodation, and the fundi were entirely normal except for one small hemorrhage in the left retina. Other than bloody crusts in both nares and one petechial hemorrhage in the buccal mucosa examination of the upper respiratory tract was within normal limits. There was no generalized lymphadenopathy. Examination of the chest revealed dullness to percussion, decreased tactile and vocal fremitus and absent breath sounds over the right lower chest posteriorly. The heart was slightly enlarged to the left and the apical beat was forceful. The rhythm was regular. A grade II systolic murmur was localized to the apex. The abdomen was markedly distended with fluid but no organs or masses were palpable. Marked dependent edema extending up to the sacrum was present. Neurologic examination was within normal limits.

The laboratory data were as follows: Blood count: red cells 3,830,000; hemoglobin 10.7 gm.; white cells, 8,150; differential count: basophiles 1 per cent, eosinophiles 4 per cent, stab forms 2 per cent, segmented forms 67 per cent, lymphocytes 25 per cent, monocytes 1 per cent. Urinalysis: specific gravity, 1.020; albumin, trace; sugar, negative; sediment, negative; urine culture, positive for coliform organisms. Stool examination: negative. Blood chemistry: non-protein nitrogen, 20 mg. per cent; calcium, 8.4 mg. per cent; phosphorus, 3.3 mg. per cent; total protein, 5.4 gm. per cent; albumin, 2.8 gm. per cent; globulin, 2.6 gm. per cent; chlorides, 101 mEq./L; potassium, 3.8 mEq./L; carbon dioxide combining power, 21.6 mEq./L; icterus index, 64 units; cephalin-cholesterol flocculation test, 4+; thymol turbidity, 6.5 units;

alkaline phosphatase, 8 Bodansky units; sodium bilirubinate, 7.9 mg. per cent; bilirubinglobin, 10.02 mg. per cent; cholesterol, 0; prothrombin time, 9.5 per cent of normal. Blood cultures: negative. Roentgenogram of the chest: the findings were consistent with the presence of right pleural, interlobar and mediastinal effusions and right lower lobe pneumonitis. Electrocardiogram: within normal limits.

On the first hospital day the patient complained of nausea and vomited small amounts of liquid material; she continued to be troubled by nausea and vomiting throughout her hospital stay. On the third day a thoracentesis was performed and 300 cc. of dark amber fluid were removed. The fluid had a specific gravity of 1.007, a protein content of 0.6 gm. per cent and contained 200 cells. Three thousand cc. of fluid with similar characteristics were removed from the peritoneal cavity. Cultures of both pleural and ascitic fluids were negative.

Because the patient's temperature rose to 38.5°c., penicillin and streptomycin therapy were instituted. Her temperature fell to normal promptly. On the fourth hospital day she vomited dark and bright blood, and her blood pressure fell to 114/50. On that day the venous pressure was 135 mm. of saline and the circulation time with decholin eight seconds. The prothrombin time was again 9.5 per cent of normal. A second cholesterol determination revealed a level of 29 mg. per cent. Repeat blood studies showed a red blood cell count of 3,700,000 with 10 gm. of hemoglobin. The white cell count was 27,000 with 9 stabs and 87 segmented forms in the differential count. On the sixth hospital day another chest x-ray revealed a marked decrease in size of the pleural effusion.

One week after entry the patient's temperature was 37.5°c, pulse 90 and blood pressure 160/90. During the first hospital week she had received large amounts of vitamin K parenterally, but because the prothrombin level failed to rise, therapy with vitamin K_1 oxide was instituted. No decrease in the prothrombin time resulted. The patient's jaundice continued unabated, and although she vomited frequently she was able to take some food by mouth. She complained frequently of vague abdominal distress, and her abdomen gradually enlarged in size. Subsequent blood chemical determination showed little change from the values recorded on entry. In addition to the therapy indicated, the patient received intravenous aureomycin, daily infusions of 50 grams of salt free albumin, 10 per cent glucose in water with added vitamins of the B complex and intramuscular crude liver extract. Early in the second hospital week the patient's prothrombin time was 15 per cent of normal. She began to exhibit twitching about the corners of the mouth, and was somewhat restless and irrational. The twitching was controlled by the intravenous injection of calcium gluconate. After several infusions of salt-free albumin the total protein rose to 5.6 gm per cent, with 4.2 gm. per cent of albumin and 1.4 gm per cent of globulin. The calcium was 9.9 mg per cent, the phosphorus 3.6 mg. per cent.

On the tenth hospital day a large subcutaneous swelling appeared over the right lung base posteriorly; it was presumed to be due to hemorrhage at the site of the thorancentesis. The patient's red blood cell count at this time was 2,940,000, the hemoglobin 8.7 gm. and the white cell count normal. Additional blood transfusions were administered. Urinalysis revealed albuminuria and the sediment contained red cells, white cells and casts. Despite adequate intake of fluid, the patient's urinary output fell markedly and in one twenty-four-hour period was only 60 cc. Edema of the face and extremities persisted. As the abdomen became distended the patient complained of marked generalized pain which was relieved by paracentesis with removal of 3,000 cc. of clear fluid. The patient was frequently lethargic and at times was noted to be irrational and restless.

Toward the end of the second hospital week she lapsed into coma. At that time her temperature was normal, pulse 124, respirations 26 and blood pressure 170/70. Examination of the heart and lungs was within normal limits. The prothrombin time was 12.5 per cent of normal. The icterus index was 100 units, and the cholesterol 62 mg. per cent. The other blood chemical values were unchanged. On the day before her death the patient's temperature began to rise and a few rales were audible. She had minor convulsive seizures and her blood pressure rose to 210/100. Following the administration of 10 cc. of a 25 per cent solution of magnesium sulfate intramuscularly there was a reduction in the frequency of the convulsive movements. On the sixteenth hospital day, September 30, 1951, the patient's temperature rose to 41°c., increasing numbers of rales and rhonchi were heard and she expired.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This patient did not present a diagnostic problem in the usual sense of the word; I believe we would all agree that she suffered from some form of hepatitis. She had been well except for an upper respiratory infection six months before admission, and two months after apparent complete recovery from the respiratory infection she began to have edema. She did not become acutely ill, however, until three weeks before admission. At that time she was seen in an outside hospital where a diagnosis of nephritis was made, understandably in view of the fact that she had edema, albuminuria and hypertension. She was deeply jaundiced when admitted to the Barnes Hospital; here her disease was rapidly progressive and she died in two weeks. Dr. Shank, will you open the discussion by considering the possible etiology of this patient's liver disease.

DR. ROBERT E. SHANK: I believe that this patient died of subacute hepatic necrosis; and if one considers the possible causes of that pathologic lesion, those which loom most prominent are homologous serum hepatitis, epidemic viral hepatitis and toxic hepatitis. As was indicated in the protocol, careful investigation was made in an attempt to determine whether the patient could have had homologous serum hepatitis. She had not received parenteral injections nor had she been subjected to needle puncture prior to the onset of her symptoms. Similarly, no evidence could be obtained to suggest that the patient had been exposed to any hepatotoxin. By exclusion, then, epidemic viral hepatitis remains as the most likely cause of her liver disease.

DR. ALEXANDER: May one distinguish, on clinical grounds, between subacute hepatic necrosis due to viral hepatitis or to toxic hepatitis?

DR. SHANK: I think not.

DR. ALEXANDER: Is it possible to distinguish early in the course of the disease those cases of viral hepatitis which will go on to subacute necrosis?

DR. SHANK: Although there have been claims in the literature to the contrary, I doubt that one can predict the ultimate outcome of epidemic hepatitis on the basis of the signs and symptoms during the very early stages of the disease.

DR. SEYMOUR REICHLIN: In terms of the prognosis of epidemic viral hepatitis it has been reported that the disease may follow an especially severe and often fatal course in adolescent girls[1] and in post-menopausal women.[2]

DR. ALEXANDER: Does the pathologic picture of viral hepatitis differ from that of toxic hepatitis?

DR. SHANK: It is my understanding that phosphorus and carbon tetrachloride in particular give rise to specific hepatic lesions which the pathologists can frequently differentiate from those of viral hepatitis.

DR. ALEXANDER: Is it possible that we are being exposed to more hepatotoxins than previously? Recent evidence in experimental animals suggests that under certain circumstances aureomycin may damage the liver,[3] and one might ask whether the introduction of the various other antibiotics, insecticides, solvents and other chemical agents may constitute a new hazard so far as liver disease is concerned. Dr. Moore, do you believe there has been an increase in toxic hepatitis recently?

DR. CARL V. MOORE: I have not been aware of it, Dr. Alexander.

DR. ALEXANDER: Is cinchophen still considered hepatotoxic, Dr. Shank?

DR. SHANK: I think it must certainly be so considered. Under certain circumstances DDT may also produce liver disease.

DR. ALEXANDER: I raised the question in regard to cinchophen because of the fact that some years ago a number of cases of hepatitis was attributed to its use. The agent had been employed widely, but because of the question of toxicity it fell into disrepute. It may be that some of the cases of hepatitis attributed to cinchophen were possibly examples of viral epidemic hepatitis. Nonetheless, I would agree with Dr. Shank that cinchophen must be considered damaging to the liver because there have been some instances in which hypersensitive-like responses to cinchophen have occurred, and in some of these, death has resulted.

DR. W. BARRY WOOD, JR.: Dr. Alexander, would Dr. Scott comment on arsphenamine

[1] BONGIOVANNI, A. M. and EISENMENGER, W. J. Adrenal cortical metabolism in chronic liver disease. *J. Clin. Endocrinol.*, 2: 152, 1951.

[2] JERSILD, M. Infectious hepatitis with subacute atrophy of the liver. An epidemic in women after the menopause. *New England J. Med.*, 237: 8, 1947.

[3] LEPPER, M. H., ZIMMERMAN, H. J., CARROLL, G., CALDWELL, E. R., JR., SPIES, H. W., WOLFE, C. K. and DOWLING, H. F. Effect of large doses of aureomycin, terramycin and chloramphenicol on liver of mice and dogs. *Arch. Int. Med.*, 88: 284, 1951.

jaundice in relation to the problem of liver damage.

DR. VIRGIL SCOTT: It now seems fairly clear that there are really two types of so-called arsphenamine jaundice. Probably the great majority of cases attributed to arsphenamine were due to the virus of homologous serum hepatitis transmitted by inadequately sterilized needles and syringes. There is certainly also a toxic form of hepatitis, early in onset, caused by arsphenamine, but it is probably responsible for only a minority of the cases of jaundice originally attributed to the drug.

DR. ALEXANDER: Comments similar to those which have been made in regard to cinchophen and arsphenamine probably could be extended to other agents which have been considered in the past to be hepatotoxins.

DR. CARL G. HARFORD: It might be suggested, Dr. Alexander, that the so-called hepatotoxic substances might act by lowering the resistance of the normal liver to viral infection. Recently, Jordan and Mirick have attempted to transmit the virus of epidemic hepatitis to mice by giving the animals substances aimed at increasing their susceptibility.[4] Some of the injected mice developed viral hepatitis, but the question as yet unsettled is whether the virus recovered was one which was latent in the mice, or whether it was the etiologic agent of the human disease.

DR. BRUCE D. KENAMORE: Although as you point out, Dr. Alexander, aureomycin has been indicted as a hepatotoxin, on the basis of certain experimental evidence it has also been used in the treatment of liver disease, the rational being that sterilization of the intestinal flora may eliminate certain endotoxins which may be damaging to the liver.

DR. ALEXANDER: Do you have any further comments in this regard, Dr. Shank?

DR. SHANK: The use of aureomycin in the treatment of cirrhosis is based on experimental work by György,[5] who found that animals, in which he attempted to produce nutritional cirrhosis, were partially although not totally protected when he included aureomycin in their feeding. This observation led to the use of the drug in human liver disease. At present I think that most investigators believe aureomycin is of little if any benefit in liver disease.

DR. ALEXANDER: Dr. Mendeloff, this patient had a number of liver function tests during her hospital stay. Would you comment on the results of these studies, and tell us whether they helped in defining the nature of the liver lesion.

DR. ALBERT I. MENDELOFF: The results of the various liver function tests were compatible with a diagnosis of severe hepatitis. Despite the fact that the patient's jaundice was of very short duration, the total bilirubin was markedly elevated, the cephalin-cholesterol flocculation test was 4+, the prothrombin level was markedly depressed and the cholesterol was very low; all of these findings indicate very serious liver impairment.

DR. ALEXANDER: The thymol turbidity was only slightly elevated. Would you comment on this finding in view of all the other abnormal liver function tests?

DR. MENDELOFF: Evidence suggests that the thymol turbidity reaction is dependent somewhat on the total blood lipid. There are those who believe that the results of this particular test afford little correlation with the severity of liver disease. In the presence of obvious severe liver disease, as was the case here, the normal thymol turbidity test indicates lack of significant regeneration of hepatic tissue.

DR. THOMAS H. HUNTER: How often in patients with hepatitis does the cholesterol fall to levels as low as were seen here? As a matter of fact, I do not recall ever having seen a patient who had no demonstrable cholesterol in the blood.

DR. SHANK: Marked depression of serum cholesterol fortunately occurs very infrequently. When it does it constitutes a very poor prognostic sign. We have not seen patients recover when the cholesterol has reached levels as low as 15 or 20 mg. per cent.

DR. MENDELOFF: We saw a young woman last year who presented a similar clinical picture, and who had a total cholesterol of 18 mg. per cent with 1 mg. per cent of cholesterol ester just prior to death.

DR. ALEXANDER: This patient had evidence of abnormal bleeding in the form of hematemeses, microscopic hematuria, petechiae and at least one retinal hemorrhage. Every effort was made to raise the prothrombin level but no success was achieved, although both vitamin K and

[4] JORDAN, J. and MIRICH, G. S. Hepatitis in mice, of presumed viral origin. *Bull. Johns Hopkins Hosp.*, 89: 326, 1951.

[5] GYÖRGY, P., STOKES, J., JR., SMITH, W. H. and GOLDBLATT, H. Studies on the use of aureomycin in hepatic disease. II. Effect of aureomycin on experimental dietary hepatic necrosis. *Am. J. M. Sc.*, 220: 6, 1950.

vitamin K_1 oxide were given. Dr. Harrington, would you discuss this problem?

DR. WILLIAM J. HARRINGTON: The choice of vitamin K preparations depends on the cause of prothrombin deficiency. When one is attempting to overcome the effect of dicumarol, either vitamin K_1 oxide, or other fat soluble preparations, such as K_1 or K_2, is the agent of choice since any of them is able to displace dicumarol from the liver. On the other hand, if one is treating a patient deficient in vitamin K because of biliary obstruction or impaired absorption, any of the water soluble synthetic vitamin K preparations is adequate. In this particular case the situation was different from either of the two enumerated. The patient had not received dicumarol and there was no reason to suspect that she suffered from clinical vitamin K deficiency. One would, therefore, have to attribute prothrombin depletion to failure of synthesis of prothrombin, despite the presence of an adequate supply of vitamin K and the absence of any antimetabolite. The available evidence indicates that in severe intrinsic hepatic disease none of the vitamin K preparations is of value.

DR. ALEXANDER: This patient received a number of blood transfusions during the course of her illness. The question is frequently asked whether there is any virtue in giving patients who are bleeding fresh blood rather than banked blood.

DR. HARRINGTON: Patients with severe liver disease have a combined deficiency of prothrombin and of accelerater (AC) globulin. If anything, the deficiency of AC globulin may be more marked than that of prothrombin. In banked blood the prothrombin concentration probably remains relatively stable, but the AC globulin is rapidly destroyed or inactivated in storage. Therefore, when blood transfusions are given to patients with severe liver disease in an attempt to restore the prothrombin time to normal, one should use fresh blood, not so much for its prothrombin content as for its AC globulin content.

DR. HUNTER: Is AC globulin available in concentrated form?

DR. HARRINGTON: Only for research purposes. Both prothrombin and AC globulin have been isolated in rather pure form and have been studied experimentally.

DR. ALEXANDER: Another deficiency which this patient exhibited was that of serum albumin. Fortunately, a supply of salt-free albumin was secured from the Red Cross, and its use resulted in a return of the serum albumin to essentially normal values. Dr. Moore, would you comment on the availability of this product?

DR. MOORE: Salt-free albumin is available from two sources. It can be bought from a commercial laboratory in ampules containing 12.5 gm. per 50 cc. At the present time such ampules cost the patient approximately $30.00 each. The Red Cross has a very limited supply of salt-free albumin which is put up in 100 cc. ampules containing 25 gm. It is supplied, if available, to patients who need it; preferably it is given to young persons, especially to those who cannot afford to buy it.

DR. ALEXANDER: Another of the problems posed by this patient—one to which we have already alluded—is the question as to whether she had renal disease *per se*. Dr. Daughaday, would you discuss this point?

DR. WILLIAM H. DAUGHADAY: The onset of this patient's illness was quite consistent with that seen in primary renal disease. Several possible explanations for this aspect of the case present themselves. Thus the patient may have had glomerulonephritis as well as hepatitis. The concomitant occurrence of albuminuria, edema and hypertension is compatible with a diagnosis of nephritis. It must be noted, however, that by the time the patient was admitted to the Barnes Hospital, the evidence for renal disease was unimpressive. This lack of findings could be interpreted, of course, to mean the patient had had nephritis which healed. Another possibility is that the patient may have been exposed to a substance toxic not only to the liver but to the kidney as well. As Dr. Shank has indicated, however, no history of such an exposure could be elicited. Finally, the urinary abnormalities could have been due to hepatic disease *per se*, but if the latter explanation is accepted it is difficult to explain the pathogenesis of the hypertension.

DR. ALEXANDER: Is azotemia a necessary component of the hepatorenal syndrome?

DR. DAUGHADAY: No, it is not. That term is rather loosely applied by some pathologists to patients with severe liver disease who also exhibit abnormal renal findings. The usual clinical picture is that of liver failure with which is associated shock, azotemia, albuminuria and oliguria.

FIG. 1. A transverse section through the liver showing collapsed and fibrotic parenchyma throughout, with large pale nodules of regenerated tissue near the hilum.

DR. ALEXANDER: You will remember that this patient did have oliguria?

DR. DAUGHADAY: Oliguria may be a feature of advanced liver disease; its mechanism is not clear at present. Apparently it is due to reversible changes in the kidney, for when liver function improves a diuresis may occur. As a matter of fact, in epidemic viral hepatitis the occurrence of a diuresis is taken by many to be a favorable prognostic sign.

DR. ALEXANDER: Do you believe that the pathologists will demonstrate significant pathologic changes in the kidneys?

DR. DAUGHADAY: In view of the history, I would be unable to rule out the possibility that the lesions of subacute glomerulonephritis will be demonstrated.

DR. ALEXANDER: What is your feeling in this regard, Dr. Goldman?

DR. MELVIN L. GOLDMAN: I believe, as Dr. Daughaday does, that one cannot rule out subacute glomerulonephritis, but I will not be surprised if no significant renal changes are present.

DR. SHANK: I would like to emphasize, Dr. Alexander, that hypertension occurred terminally in this case. The fact that hypertension is rare in liver disease constitutes additional evidence in support of a significant renal lesion.

DR. ALEXANDER: Dr. Moore, do you believe that the patient had lower nephron nehprosis?

DR. MOORE: I doubt it.

DR. ALEXANDER: Dr. Karl, you have had a wide experience with hepatic coma. Do convulsions occur commonly in liver failure?

DR. MICHAEL M. KARL: Yes, they are seen rather frequently.

DR. ALEXANDER: Have you seen hypertension in the end stage of liver disease?

DR. KARL: No, I would agree with Dr. Shank that it is rare.

DR. WOOD: Was the possibility of Weil's disease considered while the patient was in the hospital? The occurrence of abnormal bleeding, of severe hepatic involvement and possible renal impairment brings that diagnosis to mind.

DR. SHANK: We considered the possibility but did not believe that the evidence supported it.

DR. BARRETT L. TAUSSIG: I would like to ask Dr. Shank if it is not usual in severe liver disease to find increased amino acids in the serum. This patient had a normal non-protein nitrogen and I presume, therefore, that the amino acid level was likewise normal.

DR. SHANK: In the completely hepatectomized animal, the amino acids do accumulate in the blood stream. However, in the human with extremely advanced liver disease it is not common to find high amino acid levels.

DR. ALEXANDER: Dr. Daughaday, would you comment on the serum calcium values which were relatively low.

DR. DAUGHADAY: I doubt that the serum calcium was abnormal if considered in terms of the low serum protein.

DR. WOOD: Would you comment on salt metabolism in liver disease?

DR. DAUGHADAY: There is certainly a disturbance in salt excretion in patients with some types of serious hepatic dysfunction. They retain administered salt excessively as compared to normal persons. In a recent report Leslie and his associates[6] found that renal function, as measured by filtration rate, effective renal plasma flow and T_mPAH, were depressed in patients with cirrhosis at the time they were accumulating ascitic fluid.

DR. ALEXANDER: Dr. Wood, do you believe that this patient had renal disease?

DR. WOOD: I think it unlikely that she did.

DR. ALEXANDER: Everyone agrees that this patient suffered from fulminating liver disease, probably subacute hepatic necrosis following viral epidemic hepatitis. Whether or not she also had renal disease is questionable, and a

[6] LESLIE, S. H., JOHNSTON, B. and RALLI, E. P. Renal function as a factor in fluid retention in patients with cirrhosis of the liver. *J. Clin. Investigation*, 30: 1200, 1951.

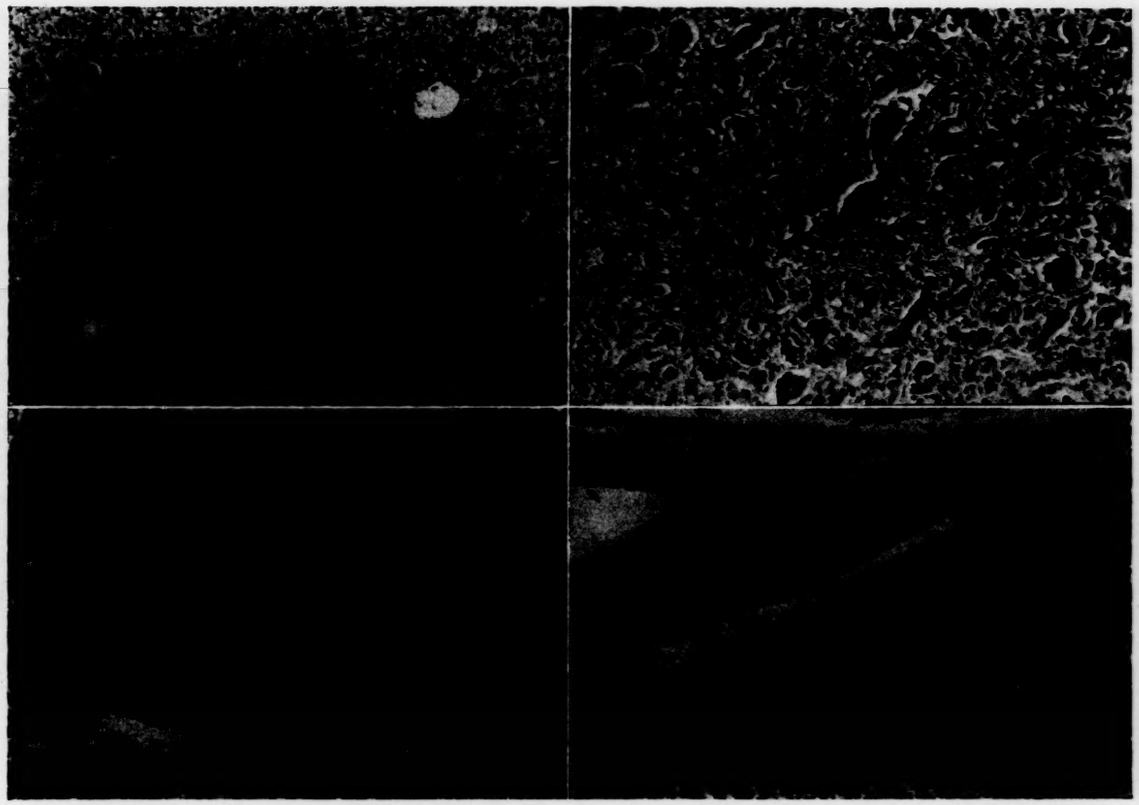


FIG. 2. A lobule of the destroyed peripheral part of the liver with loss of all apparent hepatic cells.
FIG. 3. The duct-like regenerated structures in the lobules of the liver which had the appearance of bile ducts, but were occasionally filled with bile casts indicating a cellular function similar to that of hepatic cells.
FIG. 4. A nodule of regenerated hepatic parenchyma near the hilum in which the lobular architecture is well preserved; the cells show fatty metamorphosis and bile thrombi in the canaliculi.
FIG. 5. Interstitial hemorrhage in the pancreas.

difference of opinion in this regard exists among the clinicians.

Clinical Diagnoses: Subacute hepatic necrosis secondary to viral epidemic hepatitis; ? glomerulonephritis, healed.

PATHOLOGIC DISCUSSION

DR. J. D. WHEELER: The liver was reduced to a weight of only 960 gm. The capsular surface was smooth, the cut surface soft and a large part of the parenchyma was reddish yellow with closely approximated fine vascular markings. (Fig. 1.) In the central portion near the hilum, and including both major lobes, there were bulging masses of bright yellow tissue with broad lobular patterns like those of a liver with fatty metamorphosis. The abdominal cavity contained 1,900 cc. of serosanguineous fluid. The spleen was enlarged, weighing 410 gm. The capsule was tense and the parenchyma firm and deep purplish red with obscure markings. The kidneys each weighed over 200 gm., and on the cut surface the pars convoluta was distinctly yellow and bulging. Except for this apparent fatty degeneration and slight bile-staining, the kidneys and urinary tract presented no other discernible change. The heart was essentially normal. In the lungs there were scattered focal hemorrhages in the parenchyma and slight congestion and edema. A serosanguineous hydrothorax of about 100 cc. was present in each pleural cavity. There were also extensive hemorrhages into the muscles of the abdominal and thoracic walls. The brain was not remarkable except for a moistness and mottling of the grey matter suggestive of edema.

DR. GUSTAVE J. DAMMIN: The gross appearance of the liver resembled that which was described by Lucké[7] in fatal viral hepatitis,

[7] LUCKÉ, B. The pathology of fatal epidemic hepatitis. *Am. J. Path.*, 20: 471, 1944.

which from the standpoint of gross pathology is identical with what has been called subacute atrophy with partial regeneration. The peripheral region with the reddish gross appearance had the microscopic appearance shown in Figure 2. In the upper right corner is a portal area, in the lower left a central vein. In such remnants of lobules there were areas of congestion around the central vein, and in the midzonal and peripheral portions there were irregular tubular structures which could not be positively identified either as proliferating bile ducts or regenerating hepatic cells. One reason the differentiation was difficult was that in some of these small duct-like structures which looked like bile ducts there were bile casts. The epithelium of bile ducts alone does not have the property of being able to remove the pigment from the blood, which is an essential characteristic of hepatic parenchymal cells. This conflict of appearance and apparent function complicating the identification of these structures was commented upon by Lucké in his studies. In Figure 3 there are shown some of these duct-like structures containing bile pigments, but none of the cells was of the size and configuration of hepatic cells. Figure 4 is from the regenerated area near the hilum. There were prominent bile casts in the canaliculi and many vacuoles of fat in the hepatic cells of these nodules.

A section of parenchymatous hemorrhage in the pancreas is shown in Figure 5. There was no inflammation and no evidence of a local cause for this hemorrhage or for those in the lungs and skeletal muscle. Dilatation of the pancreatic acini was also apparent, a finding which has been described as somewhat diagnostic of uremia but which has also been recognized in other conditions.

The glomeruli in many areas showed no changes except slight thickening of the basement membranes in the tuft and Bowman's capsule. There were no lesions of actual glomerulonephritis or deposition of material among the loops in the form of intercapillary glomerulosclerosis. The tubules, on the other hand, were dilated and the tubular epithelium was swollen. In some portions one could identify bile pigments in the renal tubular epithelium, and there were occasional casts. These were not, however, the lesions of lower nephron nephrosis at any stage. No diagnosis of glomerulonephritis as described by Patek, Seegal and Bevans[8] was possible; but most of the renal manifestations in this case were described in the reports by Lucké. For instance, the occurrence of albuminuria and hypertension was noted late in the disease and, interestingly enough, especially when nervous system manifestations appeared. Representative examples of blood pressure were recorded as: 144/94, 170/90, 155/70 and 150/92 among Lucké's patients, all of whom were young men of the Armed Forces.

Also in Dr. Lucké's series, fever occurred in 89 per cent of the cases and two-thirds at some stage showed ascites. In a third of that group, ascites sometimes appeared as early as ten days and quite often within twenty days after the onset of the initial clinical manifestations. Edema, although not mentioned in Dr. Lucké's series, has been said to occur in 53 per cent of cases of subchronic atrophy of the liver, and it has been suspected by some that this disease is simply a prolonged form of viral hepatitis. One explanation of the ascites which occurs so early is that the necrosis and removal of the hepatic cells allows shortening and wider opening of the intralobular sinusoids and probably their destruction, especially in the peripheral regions. This alteration effectively short-circuits the usual connections known to exist between the hepatic arterial circulation and the portal venous bed. The extensive destruction of the lobules in the majority of the liver in this case, leaving the sinusoids and the regenerating duct-like structures, illustrates how it is conceivable such a shunt could be established and be of sufficient total magnitude to raise the portal pressure. A diagnosis of portal hypertension was also favored by the fact that the spleen presented both grossly and microscopically the appearance of congestive splenomegaly.

In brief, everything we have taken from the clinical record and observed at autopsy we believe to represent manifestations that have been described in viral epidemic hepatitis.

Final Anatomic Diagnoses: Post-necrotic fibrosis of the liver with atrophy and partial regeneration limited to the hilar region; icterus; serosanguineous ascites; congestion of the spleen.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

[8] PATEK, A. J., SEEGAL, D. and BEVANS, M. The coexistence of cirrhosis of the liver and glomerulonephritis. *Am. J. M. Sc.*, 221: 77,1951.

Case Report

Paroxysmal Ventricular Tachycardia and Fibrillation Due to Quinidine*

MAXWELL J. BINDER, M.D. *and* LEON ROSOVE, M.D.
Los Angeles, California

QUINIDINE has proven to be an exceedingly valuable drug in the control of paroxysmal ventricular tachycardia since first successfully used by Scott[1] in 1921. However, on rare occasions paroxysmal ventricular tachycardia and fibrillation have been produced by the administration of quinidine.

Levy[2] reported the occurrence of paroxysmal ventricular tachycardia in five of a series of twenty-five patients with auricular fibrillation who were given quinidine in an attempt to abolish the latter arrhythmia. Kerr and Bender[3] observed the development of coupled ventricular beats, ventricular tachycardia and ventricular fibrillation following the administration of quinidine to a patient who had auricular fibrillation and complete auriculoventricular block. Lewis et al.[4] mentioned the occasional occurrence of ventricular tachycardia during quinidine therapy and reported one instance of this arrhythmia which appeared after the administration of 1.2 gm. of pure quinidine base.

Davis and Sprague[5] reported syncope and transient ventricular fibrillation, with death eight hours later, in a patient with mitral stenosis who had received moderately large doses of digitalis for cardiac failure and moderately large doses of quinidine for auricular fibrillation. Schwartz and Jezer[6] reported two patients with complete auriculoventricular dissociation who were subject to spontaneous and transient episodes of ventricular fibrillation. The intravenous injection of quinine dihydrochloride or quinidine sulfate produced transient episodes of ventricular fibrillation and syncope within one to nine minutes. Rakov[7] reported the development of fatal ventricular fibrillation in a patient who was given quinidine orally and intravenously for ventricular tachycardia which followed an acute myocardial infarction.

Hepburn and Rykert[8] reviewed twenty-six cases of ventricular tachycardia which occurred at the Toronto General Hospital over a seventeen-year period. Two of these cases were attributed to oral quinidine therapy. A similar review by Williams and Ellis,[9] covering a twenty-year period at the Boston City Hospital, resulted in the implication of quinidine in only one of the thirty-six cases reported. This patient received excessive doses of digitalis as well as large amounts of quinidine orally. Armbrust and Levine[10] reported 107 cases of ventricular tachycardia of varied etiology which occurred in the Peter Bent Brigham Hospital and in Dr. Levine's private practice over a thirty-three-year period. Two cases were attributed to quinidine. Both patients had received large doses of digitalis.

Kalmansohn and Sampson[11] reported the development of transient ventricular fibrillation in two patients following two doses of 0.2 gm. of quinidine sulfate orally. They classed these as idiosyncrasies to the drug. Sokolow and Edgar[12] reported the occurrence of paroxysmal ventricular tachycardia in a fully digitalized patient who was given moderately large doses of quinidine. A peak serum quinidine level of 15.8 mg./L. was found. Diamondstone et al.[13] reported the development of ventricular tachycardia and bilateral amaurosis in a patient who ingested a single dose of 6 gm. of quinine as a self-cure for malaria.

The following two cases are reported because of the unusual development of ventricular tachy-

* From the Medical Service, Wadsworth Hospital, Veterans Administration Center, Los Angeles. Reviewed by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions of the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

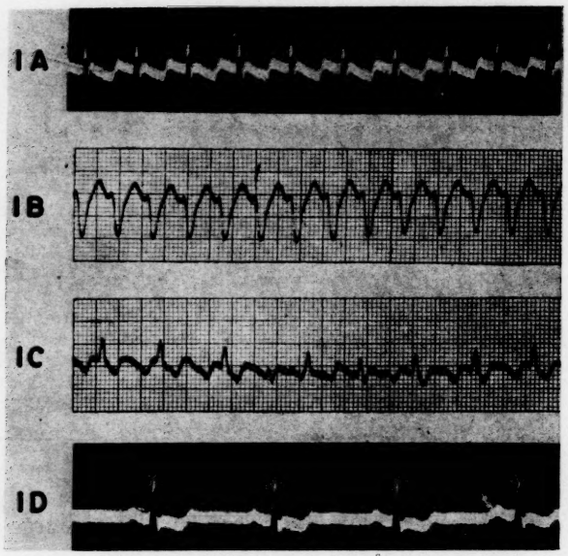


FIG. 1. Lead II of patient J. R. A, (August 25, 1949) auricular flutter; B, (September 7, 1949, 9:00 A.M.) ventricular tachycardia; C, (September 7, 1949, 2:30 P.M.) auricular flutter; D, (October 4, 1949) normal sinus rhythm.

cardia during an attempt to convert auricular flutter and auricular fibrillation to normal sinus rhythm with quinidine sulfate.

CASE REPORTS

CASE I. J. R., a sixty-nine year old white male, was admitted to Wadsworth General Hospital on August 25, 1949, because of palpitation of two hours' duration. This was associated with chest pain, dizziness and transient loss of consciousness.

He had diabetes mellitus in 1937, controlled with diet and small to moderate doses of insulin. During the six months preceding this admission his diabetes was controlled by diet alone. He had taken nitroglycerine since 1938 for moderately frequent angina. Intermittent claudication in the lower extremities had been present since 1948. During the eight years prior to admission to this hospital the patient had frequent episodes of paroxysmal auricular flutter. Some of these had stopped spontaneously; others had required quinidine sulfate therapy. Cardiac compensation remained good. Maintenance doses of quinidine, 0.8 gm. to 1.2 gm. daily, did not prevent paroxysmal auricular flutter. He was digitalized in June, 1948, but had not taken digitalis for one month prior to admission.

Physical examination on admission revealed a well developed and well nourished white male who was not dyspneic, orthopneic or cyanotic. The blood pressure was 190 mm. Hg systolic and 90 mm. Hg diastolic. Funduscopic examination revealed grade 2 arteriosclerotic changes. The thyroid was not enlarged. The heart was slightly enlarged to the left. No murmurs were heard. The heart sounds were of good quality. The heart rate was 120 per minute and the rhythm was regular. A_2 was greater than P_2. There were no signs of cardiac failure. Pedal pulses were not palpable. Both feet were cool and had a dusky hue.

The urinalysis revealed 0.5 per cent sugar and a faint trace of acetone. The red blood count was 5,700,000; hemoglobin 112 per cent; white blood count 12,600 with 76 per cent neutrophils, 22 per cent lymphocytes and 1 per cent each of monocytes and eosinophils. The sedimentation rate was 7 mm. per hour. The Kahn reaction was negative. The basal metabolic rate was minus 9 per cent. Roentgenogram of the chest showed moderate cardiac enlargement and accentuation of the pulmonary vascular markings. An electrocardiogram taken on admission revealed auricular flutter. (Fig. 1A.)

A course of quinidine sulfate therapy was started in order to convert the paroxysmal auricular flutter to normal sinus rhythm. For the first week (August 25th to September 1st) he was given quinidine 0.4 gm. three times daily. On September 2nd he received quinidine 0.2 gm. every two hours for six doses and on September 3rd and 4th quinidine 0.2 gm. every three hours for eight doses. On September 5th quinidine 0.4 gm. was given every three hours for seven doses. Auricular flutter persisted and the ventricular rate was 120 per minute and regular. On September 6th quinidine 0.6 gm. was given every three hours for eight doses, totalling 4.8 gm. in twenty-four hours. Following the last dose the patient complained of rapid heart action, visual disturbance, chest pain and increasing dyspnea. The ventricular rate was 200 per minute and regular. Fine moist rales were heard at both lung bases. Venous pressure was 19 cm. of water and rose to 29 cm. of water with right upper quadrant pressure. Arm to tongue (decholin) circulation time was 20 seconds. An electrocardiogram now showed ventricular tachycardia. (Fig. 1B.) The patient was given oxygen by means of a BLB mask. Atropine sulfate 0.8 mg. and sodium luminal 0.1 gm. were given subcutaneously. Procaine hydrochloride, 0.5 gm. in 500 cc. of 5 per cent glucose, was given intravenously with no effect. He was then given papaverine hydrochloride 0.12 gm. intra-

muscularly. By 2:30 P.M., five hours after the beginning of the ventricular tachycardia, his ventricular rate had fallen to 120 and was irregular. An electrocardiogram revealed auricular flutter with varying ventricular response. (Fig. 1C.)

The patient was digitalized on September 8th. Digitalis was continued during the remainder of his hospital stay. On each of the next six days he received quinidine 0.4 gm. every three hours for eight doses. Auricular flutter persisted with a ventricular rate of 60 to 80 per minute. On October 4th, twenty-one days after his last dose of quinidine and forty days after the onset of this episode of auricular flutter, he spontaneously reverted to normal sinus rhythm. The electrocardiogram then showed myocardial changes with a pattern of left ventricular strain and digitalis effect. (Fig. 1D.)

He remained in the hospital until February 1, 1950, receiving therapy for peripheral vascular disease. The diabetes was controlled without the use of insulin.

Discharge diagnoses were (1) arteriosclerotic heart disease with anginal syndrome and paroxysmal auricular flutter; (2) paroxysmal ventricular tachycardia due to quinidine sulfate; (3) systolic hypertension; (4) arteriosclerosis obliterans; (5) diabetes mellitus.

CASE II. J. R. G., a fifty-nine year old white male, was admitted to Wadsworth General Hospital on April 19, 1948, with complaints of palpitation and gradual onset of dyspnea and orthopnea of four days' duration. He had difficulty in sleeping and obtained relief in the sitting position. He denied chest pain, nausea and vomiting. He had three fainting spells in 1945 at which time he was told that he had no heart disease. There was no history of syphilis, rheumatic fever, chorea or scarlet fever.

Physical examination revealed a well developed and well nourished white male in moderate distress, dyspneic, but showing no cyanosis or orthopnea. The pupils were equal, regular and reacted to light and accommodation. The fundi showed increased A-V ratio, tortuosity of the vessels and slight vein compression. The thyroid was not enlarged. The blood pressure was 125 mm. Hg systolic and 85 mm. Hg diastolic; the pulse was irregular and the rate was 150 per minute; respirations were 18 per minute. The area of cardiac dullness was enlarged to the left, the point of maximal impulse being in the fifth interspace 2 cm.

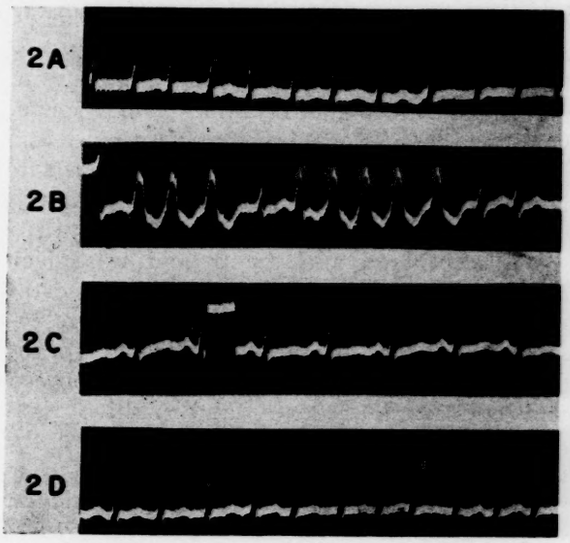


FIG. 2. Lead II of patient J. R. G. A, (April 19, 1948) auricular fibrillation with rapid ventricular rate; B, (April 26, 1948, 7:00 P.M.) auricular fibrillation with runs of paroxysmal ventricular tachycardia; C, (April 26, 1948, 8:00 P.M.) normal sinus rhythm; D, (April 30, 1948) auricular fibrillation with rapid ventricular rate.

outside the mid-clavicular line. No murmurs were heard. The sounds were totally irregular with a pulse deficit. A_2 was greater than P_2. A few scattered rales were present at both lung bases. The liver edge was firm, non-tender and felt 5 cm. below the right costal margin. There was no ascites or edema. Dorsalis pedis pulsations were palpable.

Urinalysis was negative. The blood Kahn reaction was negative. The red blood count was 5,400,000; hemoglobin 106 per cent; white blood count 8,000 with 59 per cent neutrophils, 33 per cent lymphocytes, 5 per cent monocytes and 3 per cent eosinophils. The sedimentation rate was 4 mm. per hour. The blood cholesterol was 220 mg. per 100 cc. with 63 per cent esters. The serum iodine was 6.4 micrograms per cent. Roentgenogram of the chest showed minimal cardiac enlargement with evidence of slight bilateral pleural effusion.

On admission to the hospital the patient was found to have auricular fibrillation (Fig. 2A) with evidence of early cardiac failure and minimal bilateral pleural effusion. He was given a salt-free diet, aminophylline and ammonium chloride. On April 26th quinidine sulfate was given in an effort to convert the paroxysmal auricular fibrillation to a normal sinus rhythm. The ward resident prescribed consecutive doses of 0.2, 0.4, 0.6, 0.8 and 1.0 gm. at two-hour

intervals, a total dosage of 3 gm. in eight hours. Approximately one-half hour after the last dose (1.0 gm.) was given at 5:30 P.M. the patient went into shock with cold and clammy skin, dyspnea, vomiting, convulsions, imperceptible pulse and irregular heart rhythm with a ventricular rate of 186 per minute. It was believed that this represented quinidine intoxication. The drug was discontinued and the patient was given artificial respiration and oxygen. During the period of shock the patient developed a cerebrovascular accident manifested by weakness of the right upper extremity, absent right abdominal and cremasteric reflexes, and positive right Babinski. One and one-half hours after the patient went into shock an electrocardiogram showed auricular fibrillation with ventricular rate of 170 per minute and runs of paroxysmal ventricular tachycardia. (Fig. 2B.) The patient had several Adams-Stokes attacks, requiring artificial respiration, during the following two hours. These attacks were characterized by unconsciousness, convulsions, cyanosis, cessation of respirations, inaudible heart sounds, emesis, profuse perspiration, and cold and clammy skin. At 8:00 P.M. an electrocardiogram showed a normal sinus rhythm, rate 100 per minute, with a Q-T interval of 0.38 second. (Fig. 2C.) The patient continued to vomit during the night. Gallop rhythm, moist rales at the right base and an enlarged liver palpable 7 cm. below the right costal margin were noted. The following morning (April 27th) the patient appeared improved and an electrocardiogram showed sinus rhythm and a pattern consistent with quinidine toxicity. On April 28th an electrocardiogram showed sinus rhythm with occasional supraventricular premature contractions. The Q-T interval decreased to 0.32 second and the T waves returned to a normal pattern. On April 30th auricular fibrillation with rapid ventricular rate, 160 per minute, recurred. (Fig. 2D.) Venous pressure was 20 cm. water; circulation time with calcium gluconate was fifty-five seconds and with ether twenty-eight seconds. The patient was digitalized on May 6th, with control of the rapid ventricular rate and return of cardiac compensation. He was discharged from the hospital on June 29, 1948, with the diagnoses of (1) arteriosclerotic heart disease, compensated, with auricular fibrillation; (2) paroxysmal ventricular tachycardia due to quinidine sulfate; (3) residual evidence of a cerebrovascular accident attributable to shock during quinidine toxicity.

COMMENTS

The production of ventricular tachycardia and fibrillation by quinidine has been reported in experimental animals. Drury et al.[14] found that the ventricle in dogs was quite susceptible to spontaneous ventricular tachycardia and fibrillation in the early stages of quinidine intoxication. In the later stages ventricular excitability was reduced so that little or no response was obtained with faradic stimulation. Smith et al.[15] found that large doses of quinidine given intravenously to dogs ten minutes prior to experimentally produced coronary occlusion led to the more frequent occurrence of ventricular tachycardia. However, the mortality rate from subsequent ventricular fibrillation was less in this group than in a similar group not receiving quinidine. Wégria and Nickerson[16] found that quinidine reduced the susceptibility to electronically induced ventricular fibrillation only if the dose was not too large or given too rapidly. Large doses of quinidine given rapidly led to increased susceptibility to ventricular fibrillation. Gold[17] states that quinidine and digitalis may act synergistically in this respect. In animal experiments in which the cardiac rhythm remained normal after large doses of digitalis, ventricular tachycardia was sometimes produced by small doses of quinidine. Similar doses of quinidine produced no such effect on hearts free of digitalis.

A review of the cases reported in the literature reveals a significant variation in the amount of quinidine given prior to the onset of ventricular tachycardia or fibrillation. (Table I.) However, the toxic effects of quinidine depend not only on the total dose given but also on the size of each individual dose, the interval between doses and the route of administration. Weisman[18] found that when dogs were given a large amount of quinidine in divided hourly doses the highest concentration in the heart was not more than 50 per cent of that produced by giving the same amount in one single dose. In Case II the total dose was only 3 gm. but the stepladder increase in dosage resulted in giving 1.8 gm. of quinidine in a two-hour period. The total cardiac effect of effect of quinidine and the possibility of toxicity depend in addition upon the accumulation of the drug which occurs in the first four to five days of administration.[17] Thus Case I received 4.8 gm. of quinidine in the twenty-four hours preceding the development of ventricular

tachycardia and received a total of 10.8 gm. in the four days preceding this arrhythmia.

In evaluating the role of quinidine in the production of ventricular tachycardia or fibrillation proper consideration must be given to the presence of other factors which may alone lead to these arrhythmias. The most common causes are acute myocardial infarction and digitalis. Eight of the reported cases received digitalis,[2,5,9,10,12] varying in amount from moderate[2] to excessive.[9] As pointed out by Gold,[17] doses of quinidine which are not toxic to the non-digitalized heart may be toxic to the digitalized heart. The presence of acute myocardial infarction and ventricular tachycardia prior to the use of quinidine in one of the reported cases[7] complicated the etiology of the subsequent ventricular fibrillation. Similarly, ventricular fibrillation occurred after the intravenous administration of quinidine or quinine to two patients who had spontaneously developed transient episodes of this arrhythmia prior to the use of either drug.[6] In another patient[5] numerous ectopic ventricular contractions were present after digitalization but before quinidine was used. It is possible that these ectopic contractions presaged the subsequent development of ventricular fibrillation. Quinidine may have failed to prevent but may not have caused the latter arrhythmia.

There remains a group of patients, including the two reported herein, in whom quinidine appears to be the only known factor in the production of these arrhythmias. In some instances, as in the two patients reported by Kalmansohn and Sampson,[11] an idiosyncrasy to the drug is apparently present. The possibility of coronary artery spasm was suggested by Diamondstone et al.[13] who demonstrated severe vasoconstriction in the retinal arteries of their patient. Some doubt is cast upon this latter hypothesis by the work of Elek and Katz[19] who demonstrated that toxic doses of quinidine produced profound coronary dilatation, and not constriction, in isolated fibrillating hearts of dogs.

Davis and Sprague[5] suggested that the normal integrity of the bundle tissues and Purkinje system protected against ventricular fibrillation and that disruption of this integrity by disease, injury, digitalis or quinidine might lead to

TABLE I

SUMMARY OF REPORTED CASES

Author	No. of Cases Reported	No. of Cases on Digitalis	Quinidine Dosage	Arrhythmia Produced: Ventricular Tachycardia	Arrhythmia Produced: Ventricular Fibrillation	Comments
Levy	5	3	2 gm. or less per day	+		Rheumatic heart disease in 2 patients; chronic myocarditis in 2 patients; all patients had auricular fibrillation
Kerr & Bender	1	0	0.8 gm. daily for 2 days	+	+	Auricular fibrillation and complete A-V block initially present
Lewis et al.	1	*	1.2 gm. quinidine base in 1 day	+		Further data not available
Davis & Sprague	1	1	8.2 gm. in 4 days		+	Rheumatic heart disease auricular fibrillation and numerous premature ventricular contractions prior to quinidine
Schwartz & Jezer	2	0	0.02 gm. i. v.		+	Complete A-V block with spontaneous episodes of ventricular fibrillation preceding drug
Hepburn & Rykert	2	*	**	+		Rheumatic heart disease in one patient; hyperthyroidism in one patient; both patients had auricular fibrillation
Rakov	1	0	1.3 gm. orally and 0.3 gm. i. v.		+	Acute myocardial infarction and ventricular tachycardia present prior to quinidine
Williams & Ellis	1	1	3.9 - 6.5 gm. daily for 4 days	+		Dosage of digitalis excessive
Armbrust & Levine	2	2	**	+		Both patients had auricular fibrillation
Kalmansohn & Sampson	2	*	2 doses of 0.2 gm. orally		+	Idiosyncrasy
Sokolow & Edgar	1	1	0.8 gm. every 2 hours for 4 doses	+		Rheumatic heart disease auricular fibrillation (serum quinidine level 15.8 mg /L)
Binder & Rosove	2	0	3 - 4.8 gm. in 1 day	+		Arteriosclerotic heart disease in both patients; one patient had auricular flutter and one patient had auricular fibrillation

* Not stated
** Dose not stated

ventricular fibrillation. Support is given to this theory by the work of Lenel et al.[20] and Wilburne et al.[21] who investigated epinephrine-induced ventricular tachycardia in dogs. Intravenous epinephrine produced a reflex vagal effect, probably due to stimulation of the carotid sinus by the heightened blood pressure. This resulted in sinus bradycardia, sinus standstill and partial or complete auriculoventricular block, followed with the development of paroxysmal ventricular tachycardia. This train of events could be prevented by bilateral vagotomy or by atropinization. Vagal stimulation alone resulted in interference with the higher pacemakers and with the conduction system without raising ventricular irritability, and did not result in ventricular tachycardia. Epinephrine alone, in the vagotomized animal, increased ventricular irritability without interfering with the higher pacemakers or with the conduction system and did not result in ventricular tachycardia. It was therefore concluded that the production of ventricular tachycardia by epinephrine required the simultaneous occurrence of two events (1) inhibition of the higher pacemakers and (2) increased irritability of the idioventricular pacemakers.

Toxic doses of quinidine affect the higher pacemakers and the conduction system in variable fashion. The vagal blocking action of quinidine releases these tissues from the normal vagal inhibition and leads to increased rhythmicity and conductivity. On the other hand, the direct toxic action of quinidine on these tissues results in depression of the S-A and A-V nodes and in decreased conduction through junctional tissue, the latter indicated by prolongation of the QRS complex in the electrocardiogram. The idioventricular pacemakers may thus be freed from the normal inhibitory effect of the higher pacemakers. If this occurs when the level of ventricular irritability is sufficiently high, paroxysmal ventricular tachycardia or fibrillation may result.

SUMMARY

1. Two unusual cases of ventricular tachycardia occurring during an attempt to convert auricular flutter and auricular fibrillation to normal sinus rhythm with quinidine sulfate are reported.

2. Factors which may contribute to the production of ventricular tachycardia and fibrillation by quinidine are method of quinidine administration, individual susceptibility to quinidine, prior digitalization, degree of depression of the higher pacemakers and condution system, and state of ventricular irritability.

REFERENCES

1. Scott, R. W. Observations on a case of ventricular tachycardia with retrograde conduction. *Heart*, 9: 297, 1921–22.
2. Levy, R. L. The clinical toxicity of quinidin. *J. A. M. A.*, 78: 1919, 1922. Idem. Clinical studies of quinidin. II. Alterations in the cardiac mechanism after administration of quinidin to patients with auricular fibrillation with consideration of certain toxic effects of the drug. *Arch. Int. Med.*, 30: 451, 1922. Idem. Clinical studies of quinidine. III. Some results of the quinidine treatment of auricular fibrillation. *New York State J. Med.*, 22: 276, 1922.
3. Kerr, W. J. and Bender, W. L. Paroxysmal ventricular fibrillation with cardiac recovery in a case of auricular fibrillation and complete heart block while under quinidine sulphate therapy. *Heart*, 9: 269, 1922.
4. Lewis, T., Drury, A. N., Wedd, A. M. and Iliescu, C. C. Observations upon the action of certain drugs upon fibrillation of the auricles. *Heart*, 9: 207, 1922.
5. Davis, D. and Sprague, H. B. Ventricular fibrillation: its relation to heart block. *Am. Heart J.*, 4: 559, 1929.
6. Schwartz, S. P. and Jezer, A. The action of quinine and quinidine on patients with transient ventricular fibrillation. *Am. Heart J.*, 9: 792, 1934.
7. Rakov, H. L. Ventricular fibrillation in acute coronary artery thrombosis during the intravenous administration of quinidine sulphate: report of a fatal case. *Ann. Int. Med.*, 16: 571, 1942.
8. Hepburn, J. H. and Rykert, H. E. The use of quinidine sulphate intravenously in ventricular tachycardia. *Am. Heart J.*, 14: 620, 1937.
9. Williams, C. and Ellis, L. Ventricular tachycardia, an analysis of thirty-six cases. *Arch. Int. Med.*, 71: 137, 1943.
10. Armbrust, C. A., Jr. and Levine, S. A. Paroxysmal ventricular tachycardia: a study of one hundred seven cases. *Circulation*, 1: 28, 1950.
11. Kalmansohn, R. W. and Sampson, J. J. Studies of plasma quinidine content. II. Relation to toxic manifestations and therapeutic effect. *Circulation*, 1: 569, 1950.
12. Sokolow, M. and Edgar, A. L. Blood quinidine concentrations as a guide in the treatment of cardiac arrhythmias. *Circulation*, 1: 576, 1950.
13. Diamondstone, A. H., Braveman, B. L. and Baker, L. A. Ventricular tachycardia and bilateral amaurosis produced by quinine poisoning. *Arch. Int. Med.*, 80: 763, 1947.
14. Drury, A. N., Horsfall, W. N. and Munly, W. C. Observations relating to the action of quinidine upon the dog's heart; the refractory period of, and conduction in, ventricular muscle. *Heart*, 9: 365, 1922.
15. Smith, F. H., McEachern, C. G. and Hall, G. E. The effect of the intravenous administration of quinidine sulfate on the development of ventricu-

lar fibrillation following sudden occlusion of the circumflex branch of the left coronary artery. *Am. Heart J.*, 20: 620, 1940.

16. WÉGRIA, R. and NICKERSON, N. D. Effect of papaverine, epinephrine, and Quinidine on fibrillation threshold of mammalian ventricles. *J. Pharmacol. & Exper. Therap.*, 75: 50, 1942.
17. GOLD, H. Quinidine in Disorders of the Heart. New York, 1950. Paul B. Hoeber, Inc.
18. WEISMAN, S. A. Studies on the time required for the elimination of quinidine from the heart and other organs. *Am. Heart J.* 20: 21, 1940.
19. ELEK, S. R. and KATZ, L. N. Further observations on the action of drugs on coronary vessel caliber. *J. Pharmacol. & Exper. Therap.*, 75: 178, 1942.
20. LENEL, R., VANLOO, A., RODBARD, S. and KATZ, L. N. Factors involved in the production of paroxysmal ventricular tachycardia induced by epinephrine. *Am. J. Physiol.*, 153: 553, 1948.
21. WILBURNE, M., SURTSHIN, A., RODBARD, S. and KATZ, L. N. Inhibition of paroxysmal ventricular tachycardia by atropine. *Am. Heart J.*, 34: 860 1947.

Book Reviews

Syphilis. Richard S. Weiss, M.D. and Herbert L. Joseph, M.D. 163 pages. New York, N.Y. Thomas Nelson & Sons.

With an estimated infected population of 10 per cent in the United States, syphilis is far from dead. It is with this thought in mind that this latest book on syphilology is published.

Drs. Weiss and Joseph have gathered and condensed in the 163 pages of their book much of the old and new knowledge of this disease. With the vast majority of syphilitics being treated by family physicians, this concise, readable, thorough and entirely up-to-date summation will prove invaluable to the busy general practitioner and medical student.

Syphilis is presented from its pathologic, clinical, therapeutic and preventive aspects. The subjects covered range from the technic of dark field examination to education of the general public. A very excellent summary of heavy metal and fever therapy is included, not so much because of their efficacy as for proper evaluation of late patients' past therapy and reactions. Despite the dramatic response to penicillin, the authors rightly warn against lack of proper follow-up since insufficient time has elapsed to evaluate properly the effect of the antibiotic on the late manifestations of the disease. Treatment schedules are clearly set forth. An adequate discussion of the latest concepts in immunology of syphilis is presented including false positive serologic reactions and the Treponema Immobilization Test. A small but illustrative group of photographs are included to demonstrate early and late lesions.

With medical school emphasis on syphilis relaxing, a concise presentation of this still prevalent disease's dangers and therapy is doubly welcome at this time.

R.T.

Diseases of the Nervous System. Russel Brain, M.D. 4th ed. New York, 1951. Oxford Medical Publications. *Price* $8.50.

This is the fourth edition of this text since 1933. The author attempts to keep abreast of current developments and advances in diseases of the nervous system. Frequent references from the 1949 literature have been added and a few from 1950. However, the basic organization and contents remain the same. The early portions are devoted to correlation of symptoms, clinical neuroanatomy, examination technic and demonstration of disordered function enumerating common causes of the latter.

The major portion of the book is devoted to a most useful comprehensive description and differential of the numerous disease entities and syndromes involving the nervous system according to generally accepted present day classification and terminology. A few recently recognized entities have been added and there have been minor deletions of others found in the third edition. Although the author has included the use of vitamin B_{12} in the treatment of subacute combined system disease, streptomycin in tuberculous meningitis and newer drugs for parkinsonism, therapy for other diseases is encumbered with useless remedies or outmoded or unproven forms of therapy. This is the case in the discussion of multiple sclerosis, CNS lues and poliomyelitis. Bromides are still suggested for treatment in numerous neurologic disorders including epilepsy although they have been outmoded in the latter largely by barbiturates, dilantin and other hydantoin derivatives which are considered safer and more effective.

There are several statements which will not be generally accepted. Thus the diagrams of the action of the ocular muscles are not in agreement with the more recent work of Cogan. On the basis of measurements, no actual enophthalmos is present in Horner's syndrome although this is the perpetuated classic description. Increased intracranial pressure alone is not a recognized cause of headache and there is no type of headache characteristically distinguishing it.

The book is reasonably priced and most useful for its well organized approach to the neurologic patient from the standpoint of symptoms, elucidation of signs and their correlation into a neurologic diagnosis. Most current treatment will have to be found elsewhere.

C.H., JR.

Bischoff Bulletin

No. 1

adenylic acid for systemic therapy

MY-B-DEN®

(adenosine-5-monophosphate)

The medical profession has been expressing ever increasing interest in MY-B-DEN. It is being widely used both for established indications, as well as for experimental indications and as a non-toxic source of ATP in the body. The various papers referring to adenylic acid, muscle adenylic acid, and adenosine-5-monophosphate are all based on Bischoff's MY-B-DEN and its use in adenylic acid therapy.

from the current literature on MY-B-DEN

Therapeutic Action of Muscle Adenylic Acid on Ulcers and Dermatitis Associated with Varicose or Phlebitic Veins; Preliminary Report: Rottino, A., Boller, R., and Pratt, G. H.
Angiology 1:*194, 1950**

The Control of Pruritus with Adenosine-5-monophosphate: Susinno, A. M.
Am. Pract. & Digest Treat. 2:*491, 1951**

Muscle Adenylic Acid: A Clinical Study of Its Effect: Lawrence, E. D., Doktor, D., and Sall, J.
Angiology 2:*405, 1951**

Effects of Adenine Compounds on Electrocortical Activity: Robinson, F., and Hughes, R. A.
J. Neurophysiol. 14:*387*, 1951*

The Use of Adenosine-5-monophosphate in the Pruritus of Obstructive Jaundice: Pelner, L., and Waldman, S.
Am. J. Digest. Dis. 18:*283, 1951**

Adenosine-5-monophosphate in the Treatment of Tendinitis.: Rottino, A.
Journal Lancet 71:*237*, 1951*

reprints available

Bibliography 1. Lawrence, E. D.; Doktor, D., and Sall, J.: Muscle Adenylic Acid: A Clinical Study of Its Effect, Angiology *2*:405, 1951. 2. Susinno, A. M.: The Control of Pruritus with Adenosine-5-monophosphate, Am. Pract. & Digest Treat. *2*:491, 1951. 3. Rottino, A.; Boller, R., and Pratt, G. H.: Therapeutic Action of Muscle Adenylic Acid on Ulcers and Dermatitis Associated with Varicose or Phlebitic Veins; Preliminary Report, Angiology *1*:194, 1950. 4. Albaum, H. G.; Cayle, T., and Shapiro, A.: Blood Levels of Adenine Nucleotides, J. Clin. Investigation *30*:525, 1951. 5. Robinson, F., and Hughes, R. A.: Effects of Adenine Compounds on Electrocortical Activity, J. Neurophysiol. *14*:387, 1951. 6. Rottino, A.: Relief from Pruritus Following Upon Administration of Adenylic Acid, Proc. Soc. Exper. Biol. & Med. *71*:379, 1949. 7. Kennedy, R. J.: The Treatment of Pruritus with Adenosine-5-monophosphate (Muscle Adenylic Acid), New York State J. Med. *50*:1609, 1950. 8. Rostenberg, A., Jr.; Brunner, M. J., and Riddel, J. M., Jr.: Failure of Adenosine-5-monophosphate to Affect Favorably Pruritus of Atopic Dermatitis, J. Invest. Dermat. *14*:401, 1950. 9. Sawicky, H. H.; Kanof, N. B.; Hackbarth, D. E., and Marks, I. E.: Assay VI. — Adenosine-5-monophosphate (My-B-Den) for the Relief of Pruritus, J. Invest. Dermat. *17*:265, 1951. 10. Rottino, A.: Effect of Adenylic Acid Therapy Upon Pruritus due to Hodgkin's and other Diseases, Cancer *3*:272, 1950. 11. Rottino, A.: Diagnosis and Treatment of Hodgkin's Disease, Postgrad. Med. *7*:191, 1950. 12. Matt, J. G.: The Treatment of Idiopathic Pruritus Ani with Adenosine-5-monophosphate, South. M. J. *44*:537, 1951. 13. Pelner, L., and Waldman, S.: The Use of Adenosine-5-monophosphate in the Pruritus of Obstructive Jaundice, Am. J. Digest. Dis. *18*:283, 1951. 14. Rottino, A.: The Effect of Adenosine-5-monophosphate on Pruritus, Journal Lancet *69*:285, 1949. 15. Meyer, A. E.: Die Wirkung von Cytochrom, Adenosin-5-monophosphat, Adenosintriphosphat und Adrenalin auf Schlagvolumen und Frequenz des Froschherzens, Arch. f. exper. Path. u. Pharmakol. *213*:154, 1951. 16. Rottino, A.: Adenosine-5-monophosphate in the Treatment of Tendinitis, Journal Lancet *71*:237, 1951. 17. Pratt, G. H.: Surgical Correction of Lymphedema, J.A.M.A. *147*:1121, 1951.

available dosage forms:

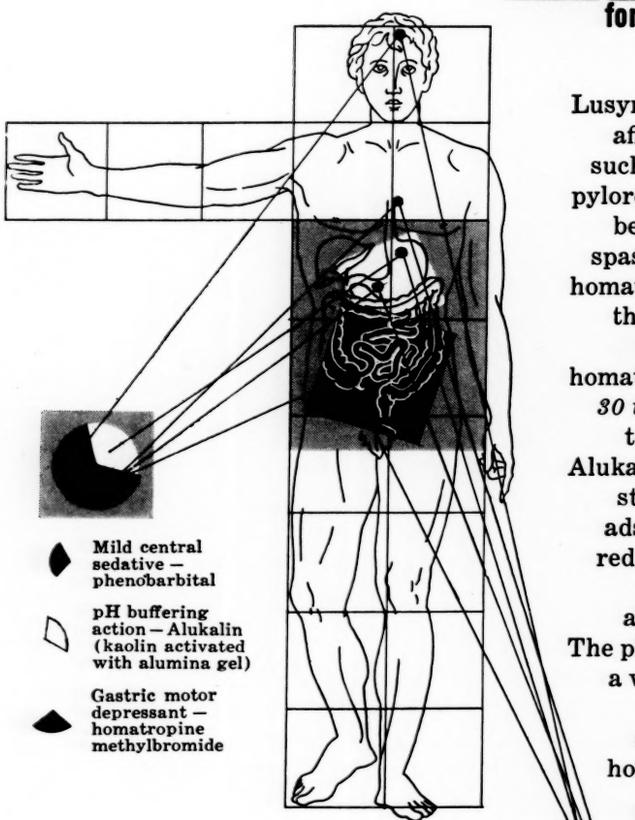
intramuscular: Sustained-Action and aqueous
oral: sublingual tablets

Bischoff

ERNST BISCHOFF COMPANY, INC • IVORYTON, CONN.
pioneers in adenylic acid therapy

SPECIALIZING *in* SPASM *in the* G. I. TRACT

not atropine —
but homatropine methylbromide for maximal safety


Mild central sedative — phenobarbital
pH buffering action — Alukalin (kaolin activated with alumina gel)
Gastric motor depressant — homatropine methylbromide

Lusyn has a particular affinity for the relief of such conditions as cardiospasm, pylorospasm and spastic colon because of the selective spasmolytic action of its homatropine methylbromide upon the gastrointestinal vagus.

Far safer than atropine—homatropine methylbromide is *30 to 50 times less likely* to produce side-effects. The Alukalin in Lusyn coats the stomach with a fine soothing adsorbent film, and helps to reduce acidity by its buffering action—without producing alkalosis or acid rebound. The phenobarbital content exerts a welcome sedative influence, and reinforces the antispasmodic effect of homatropine methylbromide.

MALTBIE LABORATORIES, INC.
NEWARK 1, N. J.

HOMATROPINE METHYLBROMIDE 2.5 mg. (1/24 gr.)
ALUKALIN (ACTIVATED KAOLIN) 300 mg. (5 gr.)
PHENOBARBITAL 8 mg. (1/8 gr.)

LUSYN®

The **NEW**

PENICILLIN COMPOUND

EFFECTIVE . . .

produces higher blood levels than oral procaine penicillin or potassium penicillin preparations in equivalent dosage

STABILITY ASSURED . . .

for 18 months at ordinary room temperature (77°F.)

PALATABLE . . .

acceptable to children and adults, no penicillin taste or aftertaste, no bulky tablets to swallow. Patients adhere to schedule

READY TO USE . . .

no tedious preparation

Note: The standard dose of Bicillin, 1 teaspoonful, supplies 300 mg. (300,000 units).

ORAL SUSPENSION

BICILLIN*

Benzethacil

N,N′-dibenzylethylenediamine dipenicillin G

Wyeth INCORPORATED, PHILADELPHIA 2, PA.

Wyeth ®

*Trademark

new hope

in

Essential Hypertension

complicated by

ATHEROSCLEROSIS-ARTERIOSCLEROSIS

***MAXITATE** with Rhamno-B_{12}, a continuing aid to a longer, normally active life, relieves symptoms of essential hypertension . . . prevents, checks and may even reverse the progress of atherosclerotic and/or arteriosclerotic development . . . maintains vascular integrity. A safe, and more complete treatment!

Maxitate with RHAMNO-B_{12}

FOR SAFE ORAL ADMINISTRATION

DESCRIPTION
Each scored Maxitate with Rhamno-B_{12} tablet contains *Maxitate 30 mg., Phenobarbital 15 mg., Rutin 30 mg., Ascorbic Acid 20 mg., Vitamin B_{12} 2 mcg.

DOSAGE—Maxitate with Rhamno-B_{12} is non-toxic—requiring no complicated dose schedule. Dosage may safely be adjusted to meet individual requirements. Recommended dose is 1 to 2 tablets every 4 hours.

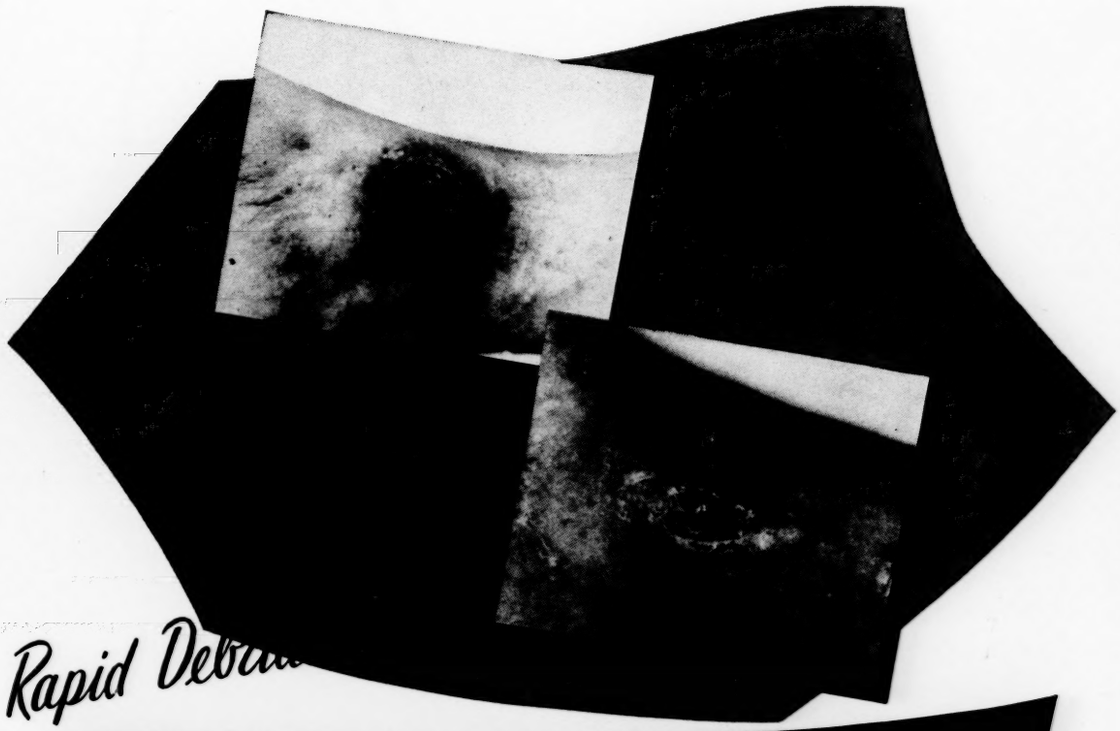
AVAILABILITY—Maxitate with Rhamno-B_{12} is available on prescription only at all leading pharmacies. Literature and supply for initiating treatment sent on request.

[illegible] STABILIZED [illegible] Rhamnol-Heteroxin, pioneered by STRASENBURGH research.

Strasenburgh

FOUNDED IN 1886

R. J. STRASENBURGH CO., ROCHESTER 14, N. Y.



Rapid Debra...

IN INFECTED WOUNDS AND CHRONIC LESIONS

INDICATIONS

General Surgical Use

- Varicose Ulcers
- Subcutaneous Hematomas
- Diabetic Gangrene
- Decubitus Ulcers
- Soft Tissue Abscesses, Sinuses, Fistulae
- Infected Compound Fractures
- Burns—Second and Third Degree
- Amputation Stumps

SUPPLIED: Tryptar powder is supplied with Tryptar Diluent, and adapter for powder blower. Write for literature on methods of application.

In chronic lesions and infected wounds, Tryptar greatly facilitates healing by removing obstacles which interfere with the natural defense mechanisms of the body. Tryptar rapidly dissolves necrotic tissue, pus and pyogenic membranes by selective proteolytic digestion, without injury to living tissue. Control of topical infection is attained.

Effective and speedy non-surgical debridement is accomplished by an entirely physiologic agent devoid of antigenic and sensitizing properties.[1]

Tryptar affords remarkable savings in medical care . . . dramatically reduces recovery time . . . shortens length of disability. Applied as powder or wet dressings.

1. Reiser, H. G., et al.; Arch. Surg. 63:568-575, 1951.

Tryptar

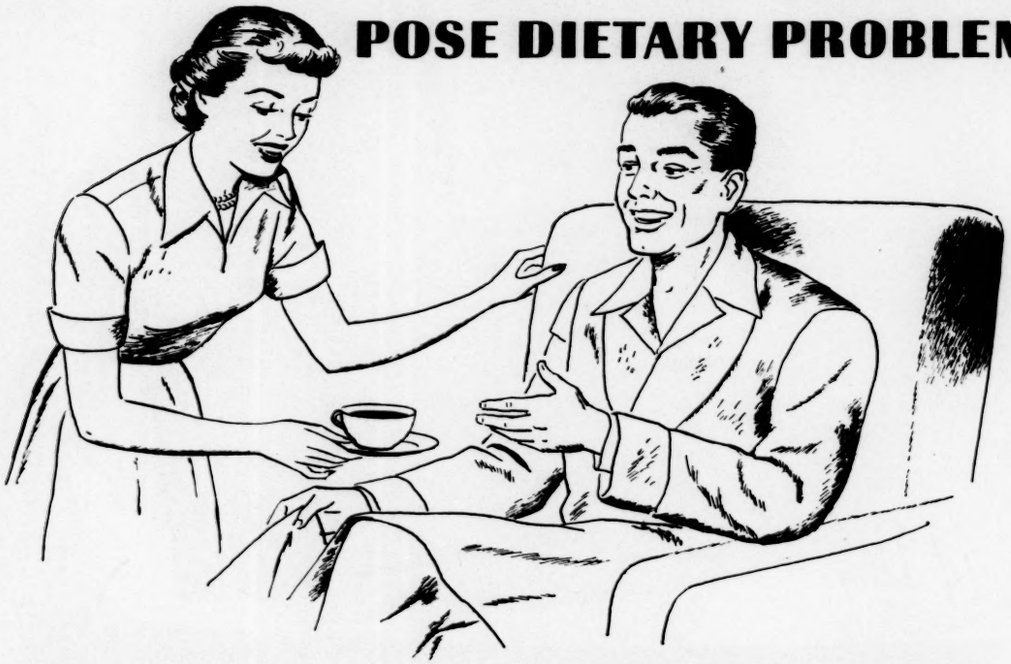
THE ARMOUR LABORATORIES BRAND OF PURIFIED CRYSTALLINE TRYPSIN

THE ARMOUR LABORATORIES • CHICAGO 11, ILLINOIS

-world-wide dependability

PHYSIOLOGIC THERAPEUTICS THROUGH BIORESEARCH

When Functional Derangements POSE DIETARY PROBLEMS



In the interest of maintaining good nutrition in the patient, many functional derangements of the gastrointestinal tract make the use of a well rounded dietary supplement, such as Ovaltine in milk, highly advantageous. Among such functional derangements more commonly encountered are nausea, anorexia, gastritis, diarrhea, dysentery, enteritis, and colitis.

In these conditions, Ovaltine in milk is particularly useful, not only because of its easy digestibility but also because of its blandness and its high nutrient content. It offers the opportunity of providing a balanced fare of essential nutrients without mechanical irritation or excessive digestive demands. Hence it qualifies especially when customarily eaten foods are contraindicated and a nutritious bland diet is required.

The wealth of nutrients supplied by three glassfuls of Ovaltine in milk is outlined in the table below.

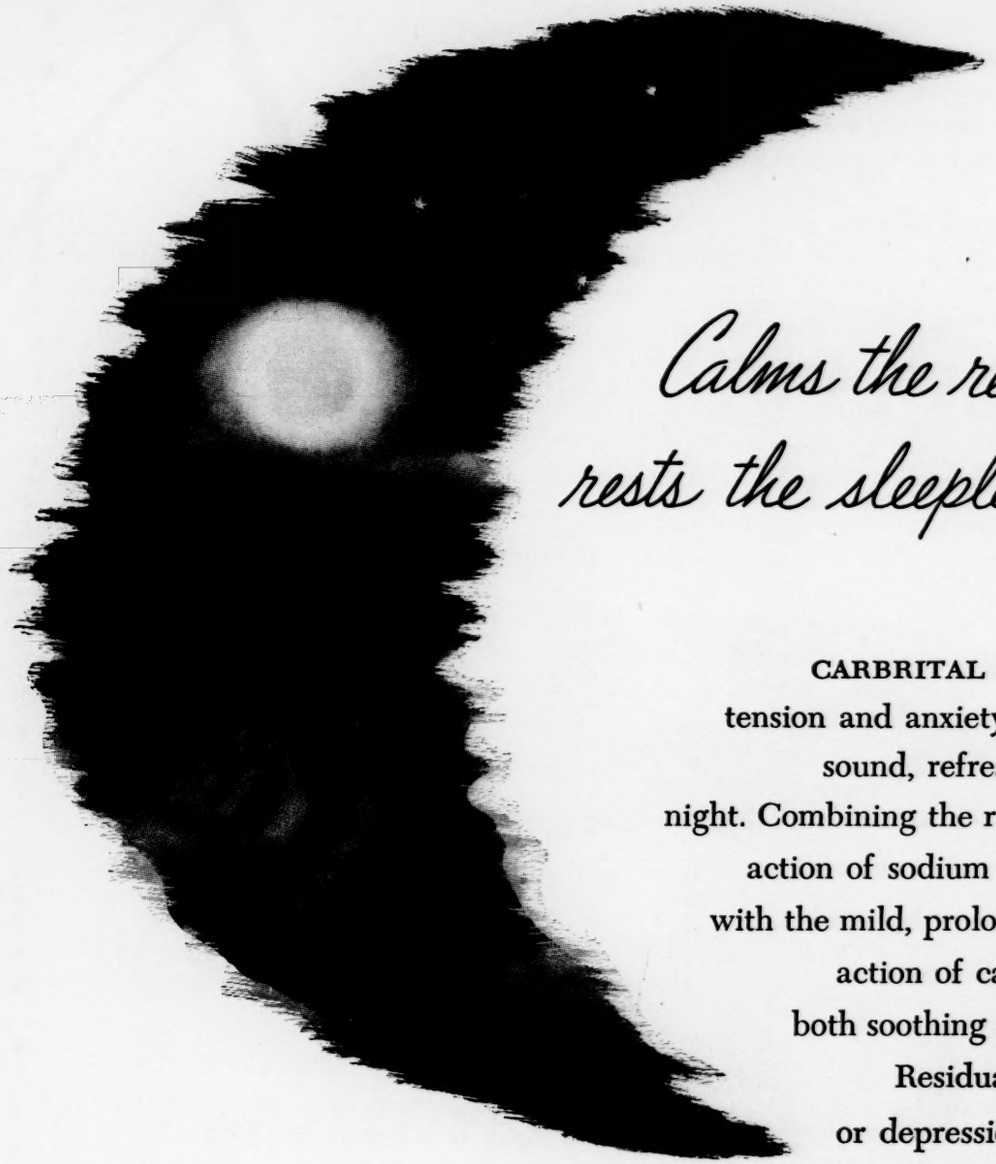
THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

Ovaltine

Three servings of Ovaltine, each made of ½ oz. of Ovaltine and 8 fl. oz. of whole milk, provide:

PROTEIN	32 Gm.	VITAMIN A	3200 I.U.
CARBOHYDRATE	65 Gm.	VITAMIN D	420 I.U.
FAT	30 Gm.	ASCORBIC ACID	30 mg.
CALCIUM	1.12 Gm.	NIACIN	6.7 mg.
COPPER	0.7 mg.	PANTOTHENIC ACID	3.1 mg.
IODINE	0.7 mg.	PYRIDOXINE	0.6 mg.
IRON	12 mg.	RIBOFLAVIN	2.0 mg.
PHOSPHORUS	940 mg.	THIAMINE	1.2 mg.
CALORIES	658		

Two kinds, Plain and Chocolate Flavored. Serving for serving, they are virtually identical in nutritional content.



Calms the restless
rests the sleepless

CARBRITAL eases daytime tension and anxiety and induces sound, refreshing sleep at night. Combining the rapid hypnotic action of sodium pentobarbital with the mild, prolonged sedative action of carbromal, it is both soothing and hypnotic. Residual "hang-over" or depression is unlikely in patients receiving **CARBRITAL**.

CARBRITAL®

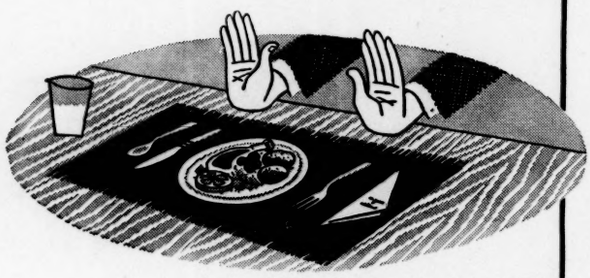
CARBRITAL is valuable for insomnia, nervous tension, and preoperative, and obstetrical sedation. It is available in two forms—Kapseal® and Elixir.

MEDICAMENTA VERA · PD & CO.

Parke, Davis + Company

When the patient

. . . sleeps poorly



. . . doesn't eat well

. . . is "always tired"

Restoration of a normal emotional picture is often facilitated by including BĒPLETE in the therapeutic regimen.

BĒPLETE®

Vitamin B-Complex with Phenobarbital Wyeth

A judicious combination of low dosage sedation and high dosage vitamin B therapy, including vitamin B_{12}.

Available as a highly palatable Elixir, and as Tablets. Also available, BĒPLETE with BELLADONNA for combined antispasmodic-sedative action; Elixir and Tablet forms.

Wyeth®
INCORPORATED
PHILADELPHIA 2, PA.

IN weight reduction

Biphetacel

"A combination of monobasic amphetamine phosphate containing a ratio of 1:3 of levo to dextro amphetamine (as found in Biphetacel), is more effective in curbing appetite and causing weight loss than the same amount of amphetamine contained in the racemic form where the ratio is 1:1 l/d. There is a relative freedom from side reactions in the patients with the 1:3 l/d combination . . . "*

Biphetacel, because of its unusual anorexic activity and relative freedom from side reactions due to the 1:3 ratio of l/d forms of amphetamine phosphate monobasic, gives maximum suppression in curbing of appetite in both vagotonic or "sluggish" and sympathicotonic or "high strung" patients, stops hunger pains, and helps to prevent constipation which frequently follows restricted caloric intake.

Each Biphetacel tablet contains the preferred 1:3 l/d ratio as provided by Racemic Amphetamine Phosphate Monobasic 5 mg. and Dextro Amphetamine Phosphate Monobasic 5 mg.; Metropine® (methyl atropine nitrate, Strasenburgh) 1 mg., Sodium Carboxymethylcellulose 200 mg.

Dosage: 1 tablet ½ hour before meals, three times daily, for the vagotonic type. Increase this dose, if necessary, to achieve the desired clinical result. ½ tablet ½ hour before meals, three times daily, for one week for the sympathicotonic type. If no signs of intolerance develop, increase this to 1 tablet. Supplied in bottles of 100 and 1000 scored tablets.

Literature and supply for initiating treatment available on request.

***Freed, S. C. and Mizel, M.—in press**

Effectively Achieves

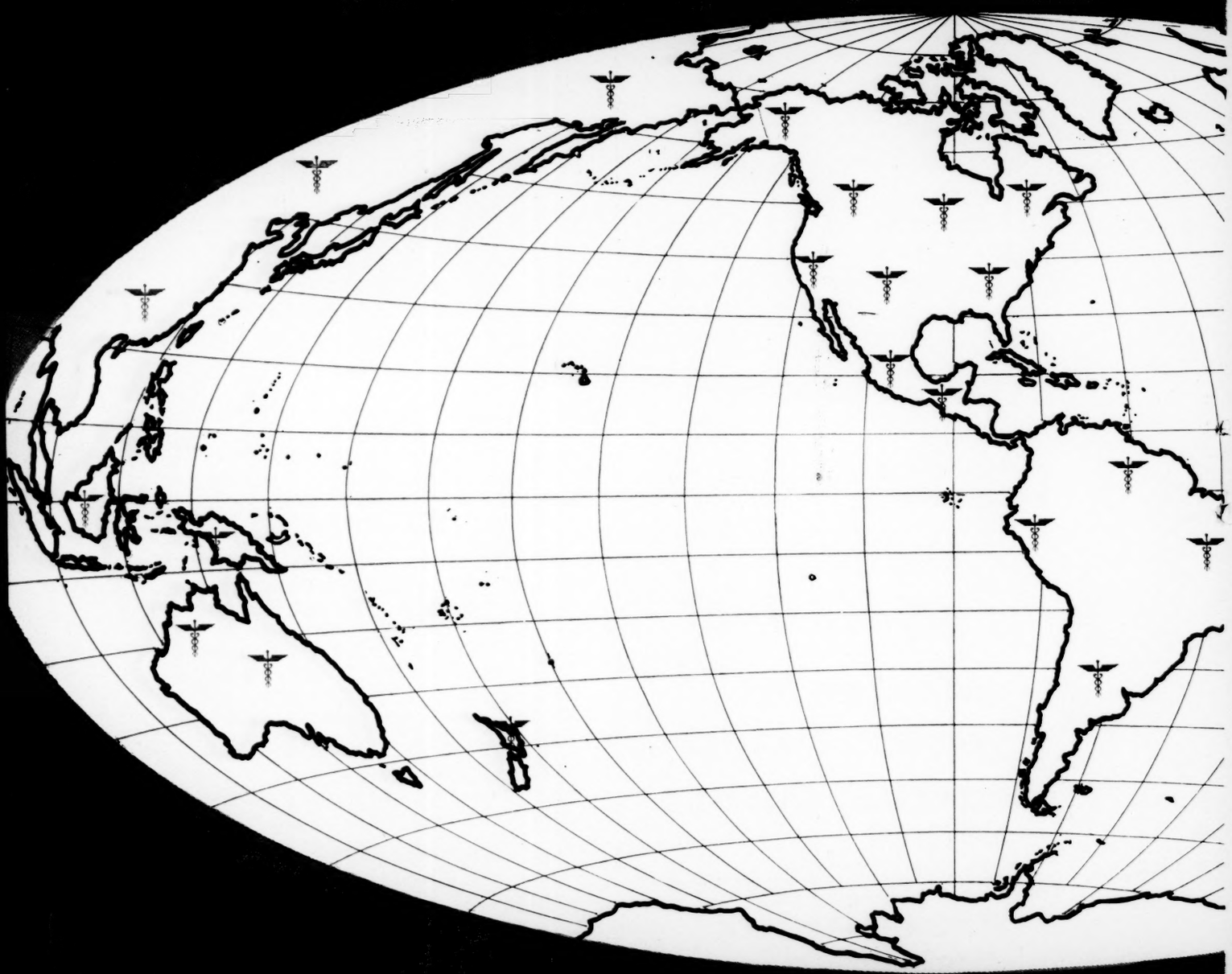
4 MAJOR OBJECTIVES...

1. **CURBS APPETITE**
2. **PREVENTS CONSTIPATION**
3. **DECREASES GASTRIC MOTILITY**
4. **PROLONGS EMPTYING TIME OF STOMACH**

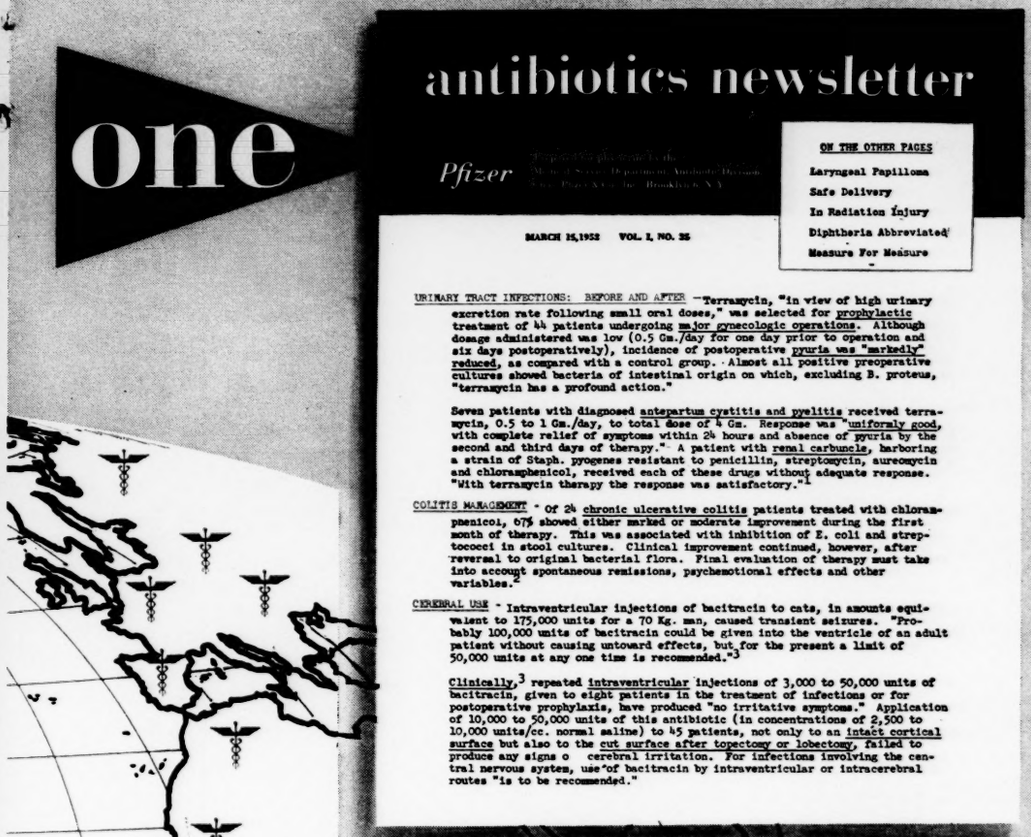
Strasenburgh

R. J. STRASENBURGH CO.
Rochester, N. Y., U. S. A.

when 600 equals



one


antibiotics newsletter
Pfizer
ON THE OTHER PAGES
Laryngeal Papilloma
Safe Delivery
In Radiation Injury
Diphtheria Abbreviated
Measure For Measure
MARCH 15,1952 VOL. I, NO. 25
URINARY TRACT INFECTIONS: BEFORE AND AFTER - Terramycin, "in view of high urinary excretion rate following small oral doses," was selected for prophylactic treatment of 44 patients undergoing major gynecologic operations. Although dosage administered was low (0.5 Gm./day for one day prior to operation and six days postoperatively), incidence of postoperative pyuria was "markedly" reduced, as compared with a control group. Almost all positive preoperative cultures showed bacteria of intestinal origin on which, excluding B. proteus, "terramycin has a profound action."
Seven patients with diagnosed antepartum cystitis and pyelitis received terramycin, 0.5 to 1 Gm./day, to total dose of 4 Gm. Response was "uniformly good, with complete relief of symptoms within 24 hours and absence of pyuria by the second and third days of therapy." A patient with renal carbuncle, harboring a strain of Staph. pyogenes resistant to penicillin, streptomycin, aureomycin and chloramphenicol, received each of these drugs without adequate response. "With terramycin therapy the response was satisfactory."[1]
COLITIS MANAGEMENT - Of 24 chronic ulcerative colitis patients treated with chloramphenicol, 67% showed either marked or moderate improvement during the first month of therapy. This was associated with inhibition of E. coli and streptococci in stool cultures. Clinical improvement continued, however, after reversal to original bacterial flora. Final evaluation of therapy must take into account spontaneous remissions, psychemotional effects and other variables.[2]
CEREBRAL USE - Intraventricular injections of bacitracin to cats, in amounts equivalent to 175,000 units for a 70 Kg. man, caused transient seizures. "Probably 100,000 units of bacitracin could be given into the ventricle of an adult patient without causing untoward effects, but for the present a limit of 50,000 units at any one time is recommended."[3]
Clinically,[3] repeated intraventricular injections of 3,000 to 50,000 units of bacitracin, given to eight patients in the treatment of infections or for postoperative prophylaxis, have produced "no irritative symptoms." Application of 10,000 to 50,000 units of this antibiotic (in concentrations of 2,500 to 10,000 units/cc. normal saline) to 45 patients, not only to an intact cortical surface but also to the cut surface after topectomy or lobectomy, failed to produce any signs o cerebral irritation. For infections involving the central nervous system, use of bacitracin by intraventricular or intracerebral routes "is to be recommended."

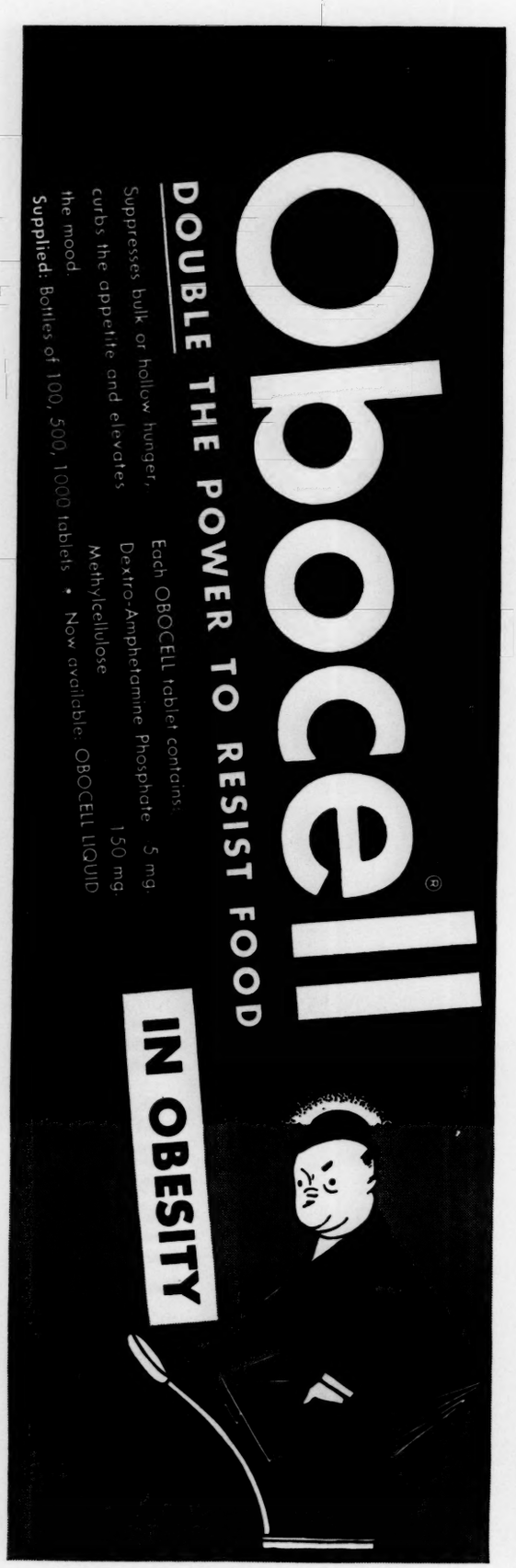
With the issue of March 15, 1952, the ANTIBIOTICS NEWSLETTER began its second year of publication. Every two weeks the ANTIBIOTICS NEWSLETTER, prepared for physicians by the Medical Service Department, brings the doctor the latest information culled from more than 600 domestic and foreign journals...plus news of antibiotic therapy and research reported at many medical meetings.

The ANTIBIOTICS NEWSLETTER is widely regarded by physicians as a ready reference to the latest information on clinical use of antibiotic agents. Concisely and objectively edited, the newsletter provides the clinician with well-rounded reports on all antibiotics in current use.

If you are not now receiving the ANTIBIOTICS NEWSLETTER *regularly, simply address your request to us at the address below.*

Pfizer

MEDICAL SERVICE DEPARTMENT • CHAS. PFIZER & CO., INC.
Brooklyn 6, N.Y.


Obocell®
DOUBLE THE POWER TO RESIST FOOD
IN OBESITY
Suppresses bulk or hollow hunger, curbs the appetite and elevates the mood.
Each OBOCELL tablet contains:
Dextro-Amphetamine Phosphate 5 mg.
Methylcellulose 150 mg.
Supplied: Bottles of 100, 500, 1000 tablets • Now available: OBOCELL LIQUID

Announcing—

The American Journal of Medicine

FIVE YEAR INDEX

July 1946 through June 1951

This new subject and author index provides an invaluable aid for quick reference and review purposes to 8,250 text pages.

Price Postpaid

$2.50 U.S.A.

$3.00 Foreign

Printing Limited—Order Today

.....ORDER FORM.....

The American Journal of Medicine, Inc.
49 West 45th Street, New York 36, N. Y.

Please send me the new Five Year Index to The American Journal of Medicine for which I enclose $2.50 U.S.A.—$3.00 Foreign

Name.....

Address.....

City.....**Zone**.....**State**.....

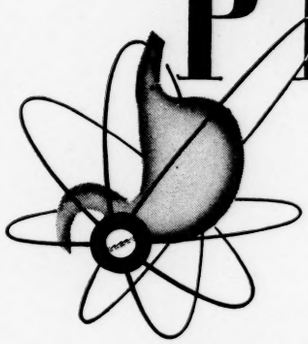
(New York City residents, add 3% sales tax)

selective
anticholinergic gives
unparalleled freedom from side effects

New

PRANTAL

Methylsulfate



for peptic ulcer

greater specificity
hitherto unobtainable freedom from side effects
wider flexibility of dosage
reduces gastric motility and secretion
relieves pain

PRANTAL* Methylsulfate is a member of an entirely new class of synthetic anticholinergic compounds. It curbs excessive vagal stimuli to the stomach by inhibiting synaptic transmission across parasympathetic ganglia.

PRANTAL Methylsulfate is unique among anticholinergic compounds. Because of its selective action, doses which reduce gastric motility and secretion rarely cause dilatation of the pupils, dryness of the mouth, urinary retention, or constipation.

The pharmacodynamics of PRANTAL Methylsulfate have been the subject of extensive laboratory investigations in which the classical procedures were used. Studies by leading clinical investigators have confirmed the value of its unusual properties in treatment of the peptic ulcer syndrome.

A Clinical Research Division monograph is now in press and will be sent to you promptly on request.

A clinical supply of PRANTAL Methylsulfate will be sent to you on request.

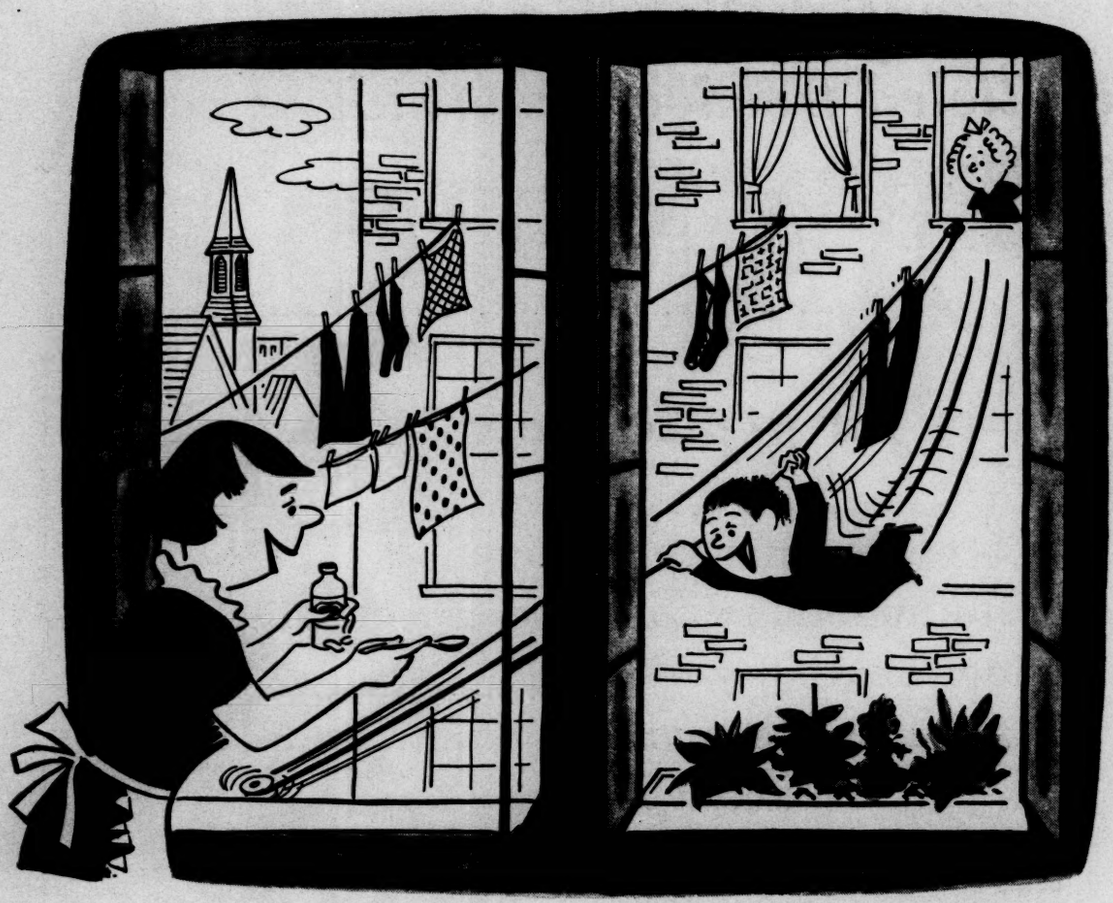
Average Dosage: One tablet (100 mg.) four times daily.

Packaging: PRANTAL Methylsulfate (brand of diphenmethanil methylsulfate), 100 mg. scored tablets, bottles of 100.

*T.M.

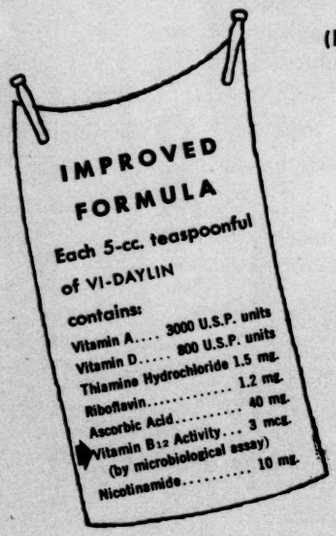
PRANTAL

Schering CORPORATION • BLOOMFIELD, NEW JERSEY



He's heard the call for VI-DAYLIN®

(HOMOGENIZED MIXTURE OF VITAMINS A, D, B_1, B_2, B_{12}, C AND NICOTINAMIDE, ABBOTT)


IMPROVED FORMULA
Each 5-cc. teaspoonful of VI-DAYLIN contains:
Vitamin A.... 3000 U.S.P. units
Vitamin D..... 800 U.S.P. units
Thiamine Hydrochloride 1.5 mg.
Riboflavin..... 1.2 mg.
Ascorbic Acid..... 40 mg.
Vitamin B12 Activity... 3 mcg.
(by microbiological assay)
Nicotinamide..... 10 mg.

POUR out a shimmering spoonful of VI-DAYLIN . . . notice its unclouded yellow-honey appearance . . . sniff its pleasant, citrus-like odor . . . then *taste* it! That delicious lemon-candy flavor explains why children accept VI-DAYLIN eagerly right from the spoon—and willingly come back for more.

NOW CONTAINS 3 TIMES THE B_{12}

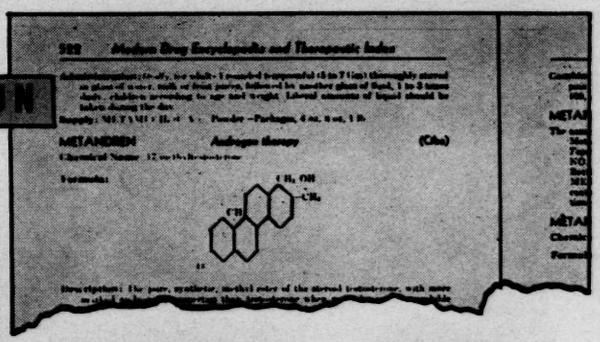
But take a look at VI-DAYLIN's improved formula. Here, truly, is effective multivitamin therapy. Seven important vitamins in every spoonful—and now three times as much vitamin B_{12}. One 5-cc. teaspoonful daily is the average dose for children up to the age of 12. Mixes with milk, juices and soft foods for infants. Stable without refrigeration. VI-DAYLIN is available at all pharmacies in 90-cc., 8-fluidounce and 1-pint bottles.

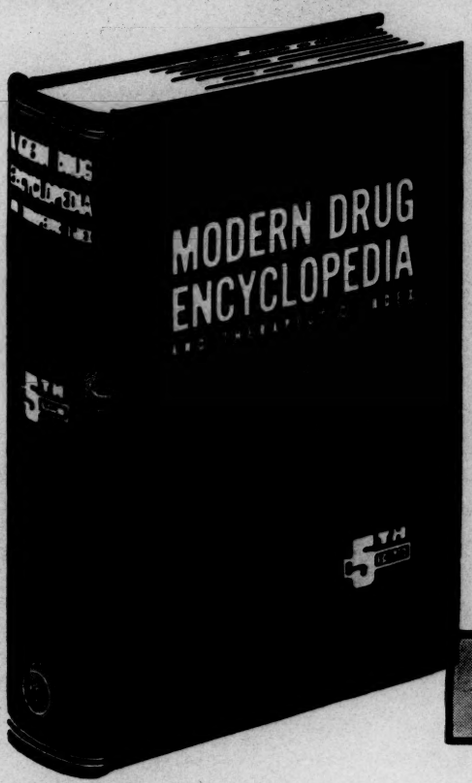
Abbott

INDISPENSABLE

for COMPLETE UP-TO-DATE REFERENCE

NEW 5TH EDITION





MODERN DRUG ENCYCLOPEDIA

AND THERAPEUTIC INDEX

Completely Rewritten to give you UP-TO-DATE, finger-tip reference on nearly 4000 Ethical Drugs (including 1500 brand new listings) of 175 manufacturers. Over 50,000 satisfied users find the MODERN DRUG ENCYCLOPEDIA is the *only* publication that provides a *complete* cross-reference desk service—the *only* encyclopedia that provides the means (through MODERN DRUGS quarterly supplements) to keep you informed of *continuing* new drug descriptions.

Edited by
MARION E. HOWARD, M.D., F.A.C.P.
Yale University Medical School

Authoritative for the latest composition, action, uses, supply, dosage—also cautions and contra-indications of thousands of new drugs. Now compiled in seven special sections: DRUGS • BIOLOGICALS • ALLERGENS • GENERIC NAME INDEX • THERAPEUTIC INDEX • MANUFACTURER'S INDEX • GENERAL INDEX.

Featuring for the 1st time—

- ★ SELF-PRONOUNCING DRUG LISTINGS
- ★ ADDITIONAL INDEX OF GENERIC DRUG NAMES
- ★ NEARLY 1500 BRAND NEW DRUG DESCRIPTIONS

MAIL THIS COUPON NOW!

Bound in Red Fabricoid. 1200 pages, size 6" x 9¼" x 2¼". Postpaid $15* U.S.A.; $18 Foreign

Complete from Description to Prescription

FREE

—to every encyclopedia owner—

MODERN DRUGS

—the quarterly supplement that keeps you up-to-date with the newest drug descriptions.

DRUG PUBLICATIONS, INC.
49 West 45th Street, New York 36, N. Y.

Enclosed is the sum of fifteen dollars ($15* U.S.A.) for which please send me postpaid the new Fifth Edition of THE MODERN DRUG ENCYCLOPEDIA AND THERAPEUTIC INDEX and MODERN DRUGS. (New York City residents please add 3% for sales tax.)

NAME _____ M.D.

ADDRESS _____

CITY _____ ZONE _____ STATE _____

*Includes three-year supplementary service at $2 per year. JMF

Hypoglossals
Sublingual, Buccal, Oral Tablets
10 mg. and 25 mg.

Descriptive Literature Available

G. W. Carnrick Co.
Newark 1, New Jersey

GERIATRIC PATIENTS

respond well to therapy with....

Androdiol

brand of diolostene (methylandrostenediol)

The new tissue-building steroid providing protein-anabolic action of androgens with minimal virilization

•

The New Approach to the Problem of Tissue-Building in Nutritional Abnormalities

•

Exerts a unique and dramatic action in effecting weight gain and sense of well-being in patients whose diets are nutritionally correct . . . cases which have not responded to dietary or other specific therapy. DMJ-18

Back Issues Wanted

(MUST BE IN PERFECT CONDITION)

THE AMERICAN JOURNAL OF MEDICINE

will pay

$1.00 per copy for the following issues:

July 1946
August 1946
September 1946
October 1946
November 1946
January 1947
February 1947
March 1947
April 1947
June 1947
July 1947
August 1947
September 1947
January, 1948
February 1948
March 1948
September 1949
November 1949
January 1951
May 1951
June 1951
July 1951
August 1951
December 1951

Send to

THE AMERICAN JOURNAL OF MEDICINE, Inc.
49 West 45th Street **New York 36, N. Y.**

Simplicity Itself

TO KEEP CARDIACS EDEMA-FREE

Effective and well tolerated, Tablets MERCUHYDRIN with Ascorbic Acid bring a new simplicity to the management of cardiac patients.

Just one or two tablets daily — plus an occasional injection — keep the average cardiac patient at basal weight. Some patients — freed of accumulated fluid with parenteral MERCUHYDRIN — may be maintained edema-free on tablets alone.

TABLETS

MERCUHYDRIN®

with ASCORBIC ACID

the simplest method of outpatient maintenance

To secure the greatest efficacy and all the advantages of Tablets MERCUHYDRIN with Ascorbic Acid, a three-week initial supply should be prescribed . . . 25 to 50 tablets.

Dosage: One or two tablets daily — morning or evening — preferably after meals.

Available: Bottles of 100 tablets. Each tablet contains meralluride 60 mg. and ascorbic acid 100 mg.

M-23

Leadership in diuretic research

Lakeside LABORATORIES, INC., MILWAUKEE 1, WISCONSIN

SQUIBB

Crysticillin Preparations

Choice for Aqueous Procaine Penicillin Therapy

Crysticillin Suspension

Squibb 300,000 Units Procaine Penicillin G in Aqueous Suspension

Crysticillin

Squibb 300,000 Units Procaine Penicillin G for Aqueous Injection

Crysticillin Fortified Duomatic

Squibb 300,000 Units Procaine Penicillin G in Aqueous Suspension plus 100,000 Units Buffered Crystalline Potassium Penicillin G in a Sterile, Two-Compartment Disposable Unit

Crysticillin Suspension Unimatic

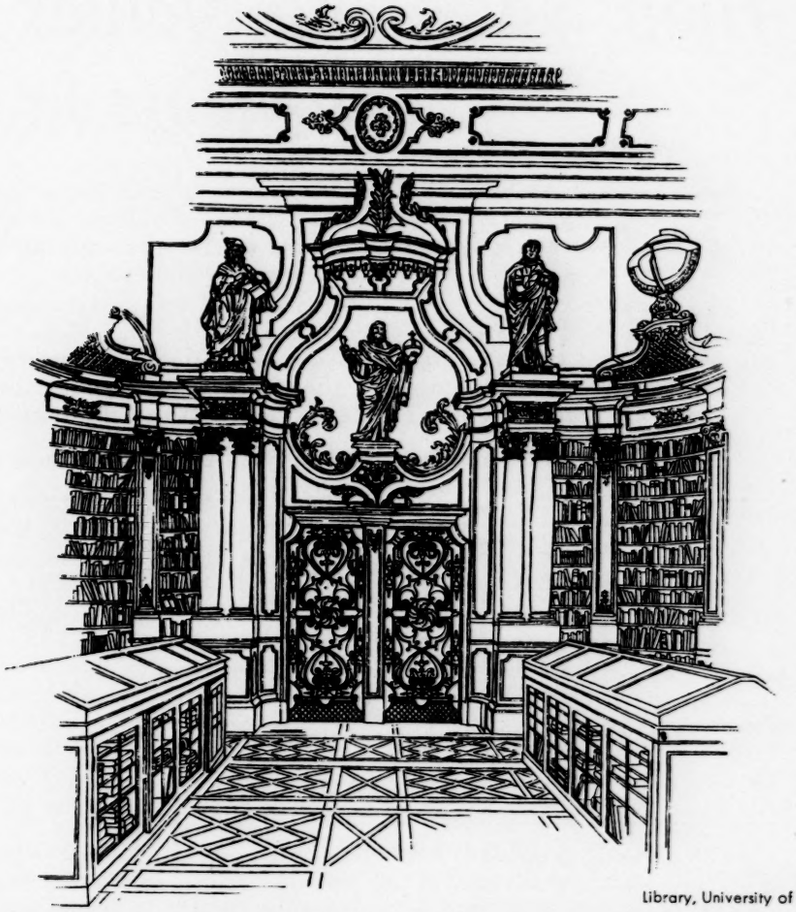
Squibb 300,000 Units Procaine Penicillin G in Aqueous Suspension in the New, Sterile Unimatic Disposable Unit — Ready to Use, Easy to Inject

Crysticillin Fortified

Squibb 300,000 Units Procaine Penicillin G and 100,000 Units Buffered Crystalline Potassium Penicillin G for Aqueous Injection

SQUIBB

'CRYSTICILLIN' (REG. U. S. PAT. OFF.), 'UNIMATIC' AND 'DUOMATIC' ARE TRADEMARKS OF E. R. SQUIBB & SONS



Library, University of Belgium

from among all antibiotics, Surgeons often choose

AUREOMYCIN

Hydrochloride Crystalline

because

Aureomycin exhibits little tendency to favor the development of resistant strains of bacteria.

Aureomycin rapidly penetrates all tissues of the body, particularly those of the gastrointestinal tract, and it has been found useful prophylactically in surgery of the tract.

Aureomycin has been reported to be effective against susceptible organisms in—

- Abscess
- Actinomycosis
- Carbuncles
- Cellulitis
- Empyema
- Furunculosis
- Gallbladder Infection
- Human Bites
- Infected Burns
- Intestinal Perforation
- Peritonitis
- Soft Tissue Infection
- Ulcerative Colitis
- Vascular Infection
- Wound Infection

Throughout the world, as in the United States, aureomycin is recognized as a broad-spectrum antibiotic of established effectiveness.

Capsules: 50 mg.—Bottles of 25 and 100. 250 mg.—Bottles of 16 and 100.
Ophthalmic: Vials of 25 mg. with dropper; solution prepared by adding 5 cc. of distilled water.

LEDERLE LABORATORIES DIVISION AMERICAN CYANAMID COMPANY 30 Rockefeller Plaza, New York 20, N.Y.

The High Nutritional Values of Meats in a Can

From the standpoint of good nutritional qualities and appetite appeal, canned meat ranks among the best of foods.[1] In nutritional values—protein, fat, vitamins, and minerals—meat preserved by modern methods of canning and meat of like variety prepared in the home virtually are interchangeable.

In canned meat, about 60 to 70 per cent of the initial thiamine content, 90 to 100 per cent of the riboflavin and of the niacin, and 70 to 80 per cent of the pantothenic acid contents are retained.[1] With due allowance for the difference in the two cuts of beef compared, the following analyses of home-cooked beef round and of canned roast beef indicate their nutritional similarity.

Composition of 100 Gm., Edible Portion

	Kitchen-Cooked Beef Round[2]	Canned Roast Beef[2]
Water	59%	60%
Calories	233	224
Protein	27 Gm.	25 Gm.
Fat	13 Gm.	13 Gm.
Minerals, total	1.3 Gm.	2 Gm.
Phosphorus	224 mg.	116 mg.
Iron	3.4 mg.	2.4 mg.
Thiamine	0.08 mg.	0.02 mg.
Riboflavin	0.22 mg.	0.23 mg.
Niacin	5.5 mg.	4.2 mg.

The canning procedure has little effect upon the biologic value of the protein of meat.[3] In a recent study of the amounts of 18 amino acids in processed meats, canned beef, pork and lamb were generally similar in amino acid composition to fresh and kitchen-cooked samples.[4] Canned meat also is an excellent source of iron.

Since thoroughly heat-processed, canned meats keep well in all climates and are economical and easy to transport, they provide a year-round reserve of meat for daily use in homes, eating establishments, institutions, and hospitals. Tremendous quantities of canned meat contribute to the food needs of our armed forces.

Conditions of modern living make canned meat one of the important foods a large segment of the American people rely upon for good nutrition. Thoroughly cooked and ready for serving at a moment's notice, meat in a can is economical both in cost and in time spent in the kitchen.

REFERENCES

1. Howe, P. E.: Foods of Animal Origin, Handbook of Nutrition, American Medical Association, ed. 2, Philadelphia, The Blakiston Company, 1951, chap. 26, p. 637.
2. Watt, B. K., and Merrill, A. L.: Composition of Foods—Raw, Processed, Prepared, Agriculture Handbook No. 8, United States Department of Agriculture, 1950.
3. Stewart, J. A., and Clark, B. S.: The Canned Food Reference Manual, American Can Company Research Division, ed. 3, New York, American Can Company, 1947.
4. Schweigert, B. S.; Bennett, B. A.; McBride, B. H., and Guthneck, B. T.: Amino Acid Content of Processed Meats, J. Am. Dietet. A. *28*:23 (Jan.) 1952.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute

Main Office, Chicago...Members Throughout the United States

No Other Hypotensive Combines these...

12 IMPORTANT FEATURES

VERILOID®

IN HYPERTENSION

Veriloid, a product of Riker Laboratories research, is an alkaloidal extract of hypotensive principles obtained by fractionation from Veratrum viride. It is freed from the dross of the mother substance. Biologically assayed in mammals, with drop in blood pressure as end point. Generically designated alkavervir.

1. Uniformly potent; constancy of pharmacologic action permits exactitude in dosage calculated in milligrams . . .
2. A unique process of manufacture produces a tablet which dissolves slowly, thus assures Veriloid absorption and action over a considerable period . . .
3. Moderates blood pressure by vasorelaxant action independent of vagomotor effect . . .
4. No ganglionic or adrenergic blocking . . .
5. Lability of blood pressure, so important in meeting the demands of an active life, is not interfered with; no danger of postural hypotension . . .
6. Cardiac output is not reduced . . .
7. No compromise of renal function . . .
8. Cerebral blood flow is not decreased . . .
9. Tolerance or idiosyncrasy rarely develops . . .
10. Hence can be given over long periods in the aim to arrest or lessen progression of hypertension . . .
11. Well tolerated in properly adjusted dosage; does not lead to headache . . .
12. Produces a prompt and sustained drop in blood pressure in all forms of hypertension.

Veriloid is available in 3 dosage forms: Veriloid (plain) in 1, 2, and 3 mg. tablets; Veriloid-VP (Veriloid, 2 mg., and phenobarbital, 15 mg.); Veriloid-VPM (Veriloid, 2 mg., phenobarbital, 15 mg., and mannitol hexanitrate, 10 mg.).

RIKER LABORATORIES, INC., 8480 BEVERLY BLVD., LOS ANGELES 48, CALIF.

In **Rheumatic** conditions

relieves muscle-spasm which causes pain

relieves pain which causes spasm

helps minimize disabling postural deformities

controls concomitant gastro-intestinal distress

Mephosal

A new whole-patient approach to the problem of pain — spasm — more pain in

low back pain, sciatica, arthritis, stiff neck, night cramps, sacroiliac distress and other common rheumatic disorders

MEPHOSAL—ELIXIR (new) and TABLETS—contains:

	each tablet	each teaspoonful (4 cc.) elixir
Mephenesin—modern, safe, non-toxic, effective skeletal-muscle antispasmodic	125 mg.	400 mg.
Sodium Salicylate—specific for rheumatic pain	125 mg.	400 mg.
Homatropine Methylbromide—safest and most efficient gastro-intestinal antispasmodic to control concomitant g.i. distress.	1.25 mg.	2.5 mg.

Average Dose: 2 or 3 tablets or one teaspoonful elixir every 3 or 4 hours.

Supplied in bottles of 50, 100 and 500 tablets. Elixir, 8 oz. and 1 pint.

Samples and detailed literature to the profession on request.

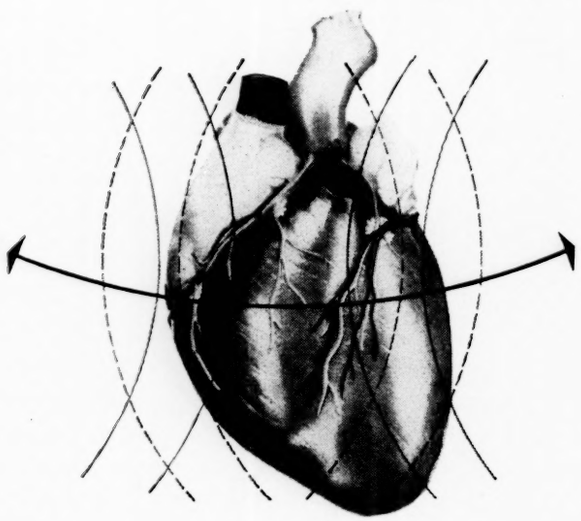
Crookes

CROOKES LABORATORIES, INC.

305 EAST 45 ST., NEW YORK 17, N.Y.

For the Overweight Patient...
Spirits Stay UP
Hunger Stays DOWN
Recognition that abnormal hunger has both a physiological and psychological basis leads to more efficient medication for the successful restraint of overeating ("the one consistent and demonstrable finding in obesity").
CYCOTIN
acts in both ways to help patients succeed.
Physiological restraint of abnormal hunger—by the non-nutritive bulk of hydrophilic methylcellulose (500 mg. per tablet).
Psychological aid in combatting the depression and anxiety that lead to compulsive overeating—by the mood-elevating action of d-amphetamine phosphate (2.5 mg. per tablet).
Average Dosage: Two tablets with water three times daily, one-half hour before meals.
Reed & Carnrick
R AND C

In cardiac decompensation



when maintenance dosage is see-sawing...

digitaline nativelle®

chief active principle of digitalis purpurea for positive, controlled maintenance

Initial compensation of the failing heart may now be accomplished in hours rather than days — but maintenance of the compensated state is often a regimen of years. Continuous adjustment of the daily cardiotonic dose, which may contribute to patient morbidity, is often obviated when a preparation of reliable, constant and unvarying potency is employed.

DIGITALINE NATIVELLE, the pioneer digitoxin, is such a preparation. It provides a uniform dissipation rate with full digitalis effect between doses. Switch your "difficult" patients to DIGITALINE NATIVELLE for smoother maintenance. Prescribe it for initial digitalization. You will be impressed with its rapidity of action and virtual freedom from local side effects.

DIGITALINE NATIVELLE is available, at all druggists, in three strengths for precise dosage — 0.1 mg. (Pink), 0.15 mg. (Blue), 0.2 mg. (White). Because of the high order of purity, most patients are adequately maintained on 0.1 mg. daily. The average dose for digitalization is 1.2 mg. in three equal doses at 4-hour intervals.

Send for brochure: "Modern Digitalis Therapy." Clinical sample available on request.

VARICK PHARMACAL COMPANY, INC. (DIVISION OF E. FOUGERA & CO., INC.) NEW YORK 13, N. Y.